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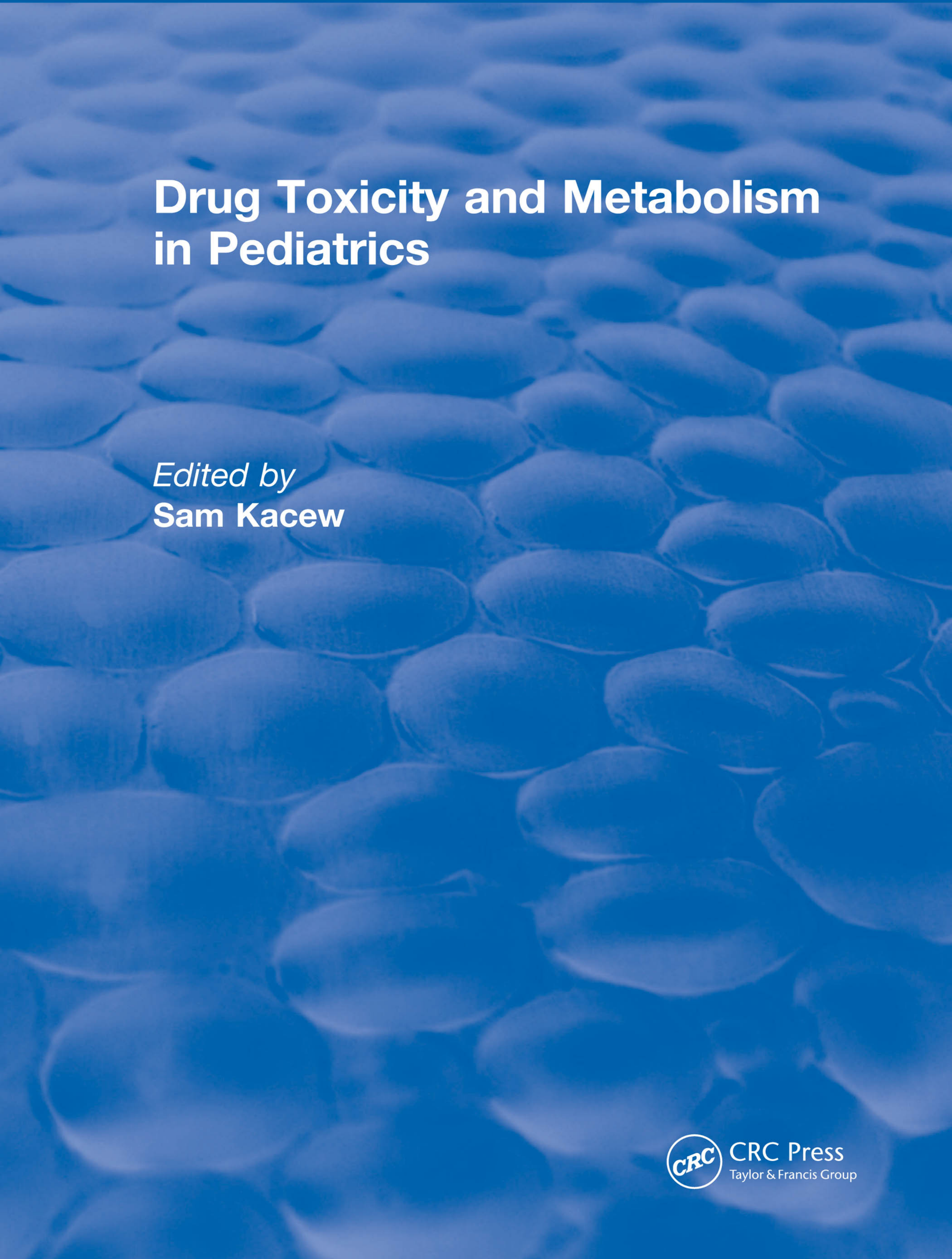

Drug Toxicity and Metabolism in Pediatrics

Edited by

Sam Kacew

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Drug Toxicity and Metabolism in Pediatrics

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PREFACE

Over the past decade, drug usage in our industrialized society has increased dramatically, especially in the pediatric population. During this tenure, it rapidly became apparent that the responsiveness of the fetus and newborn to drugs was uniquely different from that seen in the adult. The purpose of this volume is to review the pharmacokinetic and metabolic features of the newborn and fetus. This is sequentially followed by chapters dealing with drugs commonly used in pediatrics. Specifically, the pharmacology and toxicity of these drugs are described in detail with particular emphasis on the newborn and fetus.

This book is aimed not only at the pediatrician, but will also benefit the pharmacologist, toxicologist, and other health science professionals. The wide range of topics covered will interest all individuals who are concerned with the actions of drugs on humans.

It is with great pleasure that I acknowledge the dedicated and highly competent work of all contributors to this book. The efforts of the staff of CRC Press for skillful editing is greatly appreciated.

THE EDITOR

Sam Kacew, Ph.D., is Professor of Pharmacology in the Faculty of Health Sciences at the University of Ottawa, Ottawa, Ontario. Dr. Kacew received his B.Sc. degree from McGill University, Montreal, Quebec, in 1967. He obtained his M.Sc. and Ph.D. degrees in 1970 and 1973, respectively, from the Department of Pharmacology, University of Ottawa, Ottawa, Ontario. After completing postdoctoral studies at the University of Montreal, Montreal, he was appointed as an Assistant Professor of Pharmacology at the University of Ottawa in 1975. He was promoted to an Associate Professor of Pharmacology in 1980 and became a Professor in 1985.

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To Lizzie, Katherine, and Debbie.
For patience and understanding.

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TABLE OF CONTENTS

Chapter 1
Developmental Aspects of Pediatric Pharmacology and Toxicology 1
S. Kacew and S. Lock

Chapter 2
Fetal and Neonatal Drug Biotransformation 15
Mont R. Juchau

Chapter 3
Effects of Cisplatin on the Chick Embryo — A Model for the Analysis of Prenatal Toxicity 35
Roberto Narbaitz

Chapter 4
Pharmacology of Catecholamines 49
Arno Zaritsky

Chapter 5
Antidysrhythmic Drugs in Pediatrics 75
Howard C. Mofenson, Thomas R. Caraccio, Kathleen Mimnaugh, and Peter Bruzzo

Chapter 6
Diagnosis and Management of Hypertension in Pediatrics 117
Albert P. Rocchini

Chapter 7
Pharmacology and Toxicology of Loop Diuretics in Pediatrics 141
S. Kacew

Chapter 8
Chloramphenicol 155
Steven R. Abel and Martin B. Kleiman

Chapter 9
Developmental Pharmacology of Aminoglycosides and Vancomycin 173
Gideon Koren, Julia Klein, and Monica Bologa

Chapter 10
Toxicity of Antineoplastic Chemotherapy in Children 185
Theodore Zwerdling, Steven K. Bergstrom, and Stephen D. Smith

Chapter 11
Barbiturate and Nonbarbiturate Sedative Hypnotic Intoxication: An Overview 221
Joseph S. Bertino, Jr. and Michael D. Reed

Chapter 12
The Role of Doxapram in Pediatrics 233
S. Kacew

Chapter 13
Metabolism and Toxicity of Antiprostaglandin Agents 241
Cynthia J. R. Gelman and Barry H. Rumack

Chapter 14
Pharmacological and Toxicological Aspects Associated with H_1 Receptor Antagonists 251
S. Kacew

Chapter 15
Drugs in Gastrointestinal Disorders in Developing Infants 265
S. Kacew

Chapter 16
Iron Poisoning 295
Theodore G. Tong and William Banner, Jr.

Index 307

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Chapter 1

DEVELOPMENTAL ASPECTS OF PEDIATRIC PHARMACOLOGY AND TOXICOLOGY

S. Kacew and S. Lock

TABLE OF CONTENTS

I. Introduction ... 2

II. Fetal Drug Exposure During Pregnancy ... 2

III. Drugs and Breast Feeding ... 6

IV. Drugs and the Child ... 7

V. Drugs and the Older Child ... 11

VI. Summary ... 11

References ... 12

I. INTRODUCTION

The basic principles of pediatric drug therapy and toxicity were initially founded on the premise that the infant was simply a small adult. Over the last 20 years, it has been found that this concept is therapeutically inaccurate. Of necessity this has led to intensive investigation into the identification and elucidation of developmental parameters that influence clinical pharmacology. Within the field of pediatric pharmacology, it is generally accepted that there are a number of unique developmental stages which must be considered with respect to drug effect and toxicity. The developmental stages are related to the mode of exposure as follows:

1. *In utero* the fetus may be inadvertently exposed to drugs secondary to maternal chemical ingestion.
2. The neonate may encounter drugs as a result of maternal administration via the breast milk. At this stage, direct drug exposure can also occur.
3. The older infant and child are no longer subject to lactational exposure, but merely to the direct route.

As the infant develops, the mother's influence diminishes with respect to drug exposure. However, the direct route gains prominence with increasing age and can be potentially more hazardous. The aim of this chapter is to provide a general background on the influence of drugs on the developing infant.

II. FETAL DRUG EXPOSURE DURING PREGNANCY

During the course of her pregnancy, a mother is likely to take a number of drugs for therapeutic reasons. In addition, with many more women in the work force, there is an increased potential for interactions between therapeutic agents and a variety of chemicals present in the occupational environment. Furthermore, a large number of women indulge in a variety of recreational chemicals. Alcohol, as an example, is well known to influence drug action. The consequences attributed to the exposure to a pharmaceutical product should be advantageous to the mother; however, in many instances, the effects can be deleterious to the fetus. Thus, it may be stated that the fetus is at some jeopardy as a result of exposure to pharmaceutical agents.

Nutrients essential for fetal growth and development require an active transport system to be moved from the maternal circulation to the fetal circulation against a concentration gradient. By contrast, drugs cross the placenta by simple diffusion. There are a number of factors listed in Table 1 which will influence the transfer of drugs from the maternal circulation to the fetus and thus will have a bearing on any subsequent fetal manifestations. The amount of a chemical that is transferred to the fetus is dependent on lipid solubility, the degree of ionization, and the molecular weight. Lipophilic drugs tend to diffuse across the placenta readily, while highly ionized compounds penetrate the placental membrane slowly. The molecular weight of an agent affects placental transfer, with the larger molecules crossing the placental barrier less readily. Protein binding of a drug or its metabolites will affect the rate and amount that is transferred to the fetus. Exposure of fetal target tissues to chemical entities may also be influenced by metabolism in the placenta or the fetal liver.[2]

An important component to consider is the stage of fetal development at the time of chemical exposure. During the first week of development after fertilization, the embryo undergoes the process of cleavage and gastrulation. Exposure to drugs such as antimetabolites, ergot alkaloids, or diethylstilbestrol at this stage can result in termination of pregnancy.[3] Organogenesis is the next developmental stage covering weeks two to eight of

TABLE 1
Factors Affecting Placental Transfer and Fetal Drug Effects

Physicochemical properties	The ability of drugs to reach the fetus are dependent upon water solubility, lipid solubility, and molecular weight
Pharmacokinetics	Fetal effects observed are dependent upon drug concentration in fetal blood supply, placental drug metabolism, and elimination
Developmental stage	Teratogenic agents act selectively on developing cells
Duration of exposure	A single administration of a high dose of a drug can produce damage to the same extent as chronic, low-dose treatment
Genetic	Enzymic deficiency can predispose a fetus to enhanced toxicity
Drug interactions	The presence of more than one drug and/or chemical can increase susceptibility of the fetus
Environment	Various factors in the environment can modify the drug and thereby affect placental transfer

Adapted from Lock, S. and Kacew, S., *Toxicologic and Pharmacologic Principles in Pediatrics,* Kacew, S. and Lock, S., Eds., Hemisphere, Washington, D.C., in press.

TABLE 2
Relationship Between Developmental Stage and Pharmaceutical Consequence

Developmental stage	Target system	Observed effect
Placenta	Cardiovascular	Interference with active transport Alterations in maternal-fetal circulation
	Metabolism	Biosynthesis of nutrients Biotransformation of xenobiotics
Embryo	Whole organism	Intrauterine growth retardation Congenital anomalies
Fetus	Whole body	Growth retardation
	Reproductive and kidney	Genitourinary abnormalities
	Bone	Skeletal anomalies
Neonate	Central nervous system	Neurobehavioral abnormalities Withdrawal symptoms Altered mental ability
	Reproductive	Altered fertility
	Respiratory	Respiratory depression
	Musculature	Hypotonia
	Whole organism	Neonatal death

Adapted from Lock and Kacew[1] and Hill and Kleinberg.[6]

gestation. Exposure to drugs including thalidomide, alcohol, lithium, phenytoin, and isotretoin during this phase can result in serious structural abnormalities.[3-5] Chemicals such as cigarette smoke, heavy metals, or carbon monoxide may affect development during the remaining gestational period, ranging from 9 weeks to 9 months. Predominant effects are alteration in the differentiation of the reproductive and central nervous systems.[3] Consequently, altered brain function and growth retardation are some of the principle adverse effects due to exposure at this stage. The relationship between stage of development and type of effect is illustrated in Table 2.

A perspective of the potential seriousness of the problems associated with drug use during pregnancy and the consequence to the fetus is gained from examination of Tables 3 to 5. Although these tables are extensive, they are by no means all encompassing. Furthermore, some of the effects shown to occur in humans by one group of investigators could not necessarily be confirmed by other scientists. In spite of these uncertainties, any reports

TABLE 3
Maternal Drug Ingestion as a Therapeutic Measure and Fetal Effect

Drug	Fetal effects
Acetazolamide	Electrolyte imbalance, hematological changes, forelimb defects*
Amantidine	Single ventricle, pulmonary atresia, skeletal anomalies*
Aminophylline	Tachycardia, gagging, vomiting, nervousness, opisthotonos, digit defects
Aminopterin	Multiple gross anomalies, fetal death, prenatal and postnatal growth retardation, renal anomalies, craniofacial abnormalities
Androgens	Masculinization of female fetus
Atropine	Tachycardia, dilated nonreactive pupils, skeletal anomalies*, cytolytic effect on brain*
Azathioprine	Abnormal lymphocyte chromosomes at birth
β-Adrenergic agonists	Increase in fetal heart rate, fetal cardiac arrhythmias, fetal hyperglycemia, hypotension
Bromides	Postnatal growth retardation, neurobehavioral abnormalities, acneform rash
Bupivacaine	Hyperirritability, incessant crying, meconium staining, metabolic acidosis, hypotonia, apnea, methemoglobinemia
Busulfan	Intrauterine and postnatal growth retardation
Carbimazole	Goiter, hypothyroidism
Chlorambucil	Renal agenesis, various fetal abnormalities*
Chloramphenicol	Increased risk of "gray-baby" syndrome, cleft lip, cleft palate
Chlordiazepoxide	Newborn withdrawal
Chloroquine	Ototoxicity
Chlorpromazine	Extrapyramidal dysfunction, neonatal CNS depression, congenital malformations (?), GI tract dysfunction, curled toe*, intrauterine growth retardation*
Chlorpropamide	Hypoglycemia
Cimetidine	Sexual dysfunction*
Clomiphene	Meningomyelocele, decreased birth weight, multiple births
Corticosteroids	Malpositioned kidney, decreased birth weight, increased antenatal death rate, electrolyte imbalance, increased lung maturity, increased risk of infection, cleft palate*, skeletal abnormalities*
Cyclizine	Cleft palate*, micrognathia*, microstomia*
Cyclophosphamide	Digital defects, flattened nasal bridge, ectrodactyly, palatal anomalies, single coronary artery, bone marrow suppression
Cytarabine	Congenital malformations*, cleft palate*, club foot*
Dextropropoxyphene	Withdrawal symptoms
Diazepam	"Floppy" infant syndrome, newborn behavior abnormalities, cleft lip and palate (?)
Diazoxide	Hyperglycemia, hypertrichosis, languginosa, alopecia
Diethylstilbestrol	Vaginal adenocarcinoma, vaginal adenosis, penile abnormalities, epididymal cysts, hypotrophic testes, hypoplastic uterus, cervical gross defects
Ergot	Spontaneous abortion, CNS symtoms, Poland syndrome
Ethchlorvynol	Lethargy, hypotonia, neurobehavioral
Ethinyl estradiol	VACTEL anomalies, congenital heart defects, feminization of male fetus, trunoconal great vessel malformation
5-Fluorouracil	Abortion, craniofacial abnormalities
Furosemide	Delay in renal maturation*
Glutethimide	Withdrawal manifestations, increased resorption rate*
Griseofulvin	Skeletal anomalies*, eye defects*, CNS dysfunction*
Haloperidol	Extrapyramidal dysfunction, neonatal CNS depression, congenital malformations (?), GI tract dysfunction, curled toe*, intrauterine growth retardation*
Halothane	Neonatal inability to habituate to auditory stimuli
Heparin	Perinatal and neonatal mortality incidence higher than with warfarin
Hydrochlorothiazide	Thrombocytopenia, hypoglycemia, electrolyte imbalance
Hydroxyurea	Microphthalmia*, hydrocephaly*, decreased postnatal learning*, palate and skeletal defects*
Hydroxyzine	Hypotonia, nervousness, myoclonic jerks, inability to read
Idoxuridine	Exophthalmos*, club foot*
Imipramine	Respiratory difficulties, irritability, feeding difficulty, urinary retention, limb anomalies, encephaly, profuse sweating, skeletal anomalies*

TABLE 3 (continued)
Maternal Drug Ingestion as a Therapeutic Measure and Fetal Effect

Drug	Fetal effects
Indomethacin	Neonatal pulmonary hypertension, disturbed cardiopulmonary adaptation, cleft lip and palate, infant death
Insulin	Growth retardation*, skeletal anomalies*, hypoglycemia
Iodide	Goiter, abnormal neonatal thyroid function
Iodine (radioactive)	Hypothyroid, mental retardation, exophthalmos, goiter
Lignocaine	Seizures
Lithium	Congenital heart disease, goiter, hypotonia, hypothermia, neonatal cyanosis, poor sucking
Meclizine	Omphalocele, ectromelia, fetal death, cleft palate*, incomplete skeletal ossification*, macrostomia*
Mepivacaine	Fetal bradycardia
Meprobamate	Congenital heart disease, withdrawal symptoms, malformed diaphragm, behavioral abnormalities*
6-Mercaptopurine	Abortion, craniofacial abnormalities
Methaqualone	Vertebral and rib defects*
Methotrexate	Agenesis of frontal bones, cranial synostosis, abortion, unusual facies, postnatal growth retardation
Methoxyflurane	CNS depression, skeletal anomalies*
Methyltestosterone	Pseudohermaphroditism of female fetus
Methylthiouracil	Hypothyroidism, goiter
Mitomycin C	Defects of palate, skeleton, and brain*
Nitrofurantoin	Hemorrhage, anemia
Nitrogen mustard	Small malpositioned kidney, bone marrow suppression
Novobiocin	Interference with bilirubin conjugation
Oral contraceptives	Congenital heart defects, limb reduction anomalies, VACTEL anomalies
Oxytocin	Hyperbilirubinemia, delayed adaptation to extrauterine life, convulsions
Paraldehyde	Decreased adaptation to extrauterine life
Penicillamine	Abnormal connective tissue
Phenobarbital	Acute: decreased hearing capacity, CNS depression, decreased incidence of neonatal hyperbilirubinemia, hemorrhage, anemia Chronic: infant withdrawal symptoms include tremulousness, excess crying, hyperphagia, hyperacusia, fetal addiction
Phenytoin	Fetal hydantoin syndrome: craniofacial abnormalities, limb abnormalities, mental and growth deficiency, congenital heart disease and hernias, coagulation defects, neonatal hemorrhage
Procarbazine	Small, malpositioned kidney*, anencephaly*, congenital anomalies*, CNS defects*
Progestins	Masculinization of female fetus, clitoral enlargement, lumbosacral fusion, VACTEL anomalies
Propranolol	Hypoglycemia, bradycardia, apnea, prolonged labor, hypocalcemia, intrauterine growth retardation, intrapartum asphyxia
Propylthiouracil	Goiter, fetal death, hypothyroidism
Quinacrine	Increased fetal death rate*
Quinine	Mental retardation, ototoxicity, congential glaucoma, genitourinary abnormalities, fetal death, anemia
Reserpine	Nasal congestion and discharge, lethargy, hypothermia, bradycardia
Scopolamine	Lethargy, tachycardia, fever, respiratory depression
Sulfonamides	Methemoglobinemia, hemorrhage, anemia, jaundice
Tetracyclines	Tooth discoloration, enamel hypoplasia, retardation in bone growth
Thalidomide	Limb anomalies
Tolbutamide	Fetal death, failure to thrive, apneic spells
Trimeprazine	Extrapyramidal dysfunction, neonatal CNS depression, congenital malformations (?), GI tract dysfunction, curled toe*, intrauterine growth retardation*
Trimethadione	Characteristic facies (V-shaped eyebrows and low ears), cardiac anomalies, ophthalmic anomalies, developmental delay, mental deficiency, growth retardation, conductive hearing loss
Valproic acid	Spina bifida

TABLE 3 (continued)
Maternal Drug Ingestion as a Therapeutic Measure and Fetal Effect

Drug	Fetal effects
Vincristine	Small, positioned kidney*, eye defects*, cranial abnormalities*, skeletal anomalies*
Warfarin	Embryopathy includes nasal hypoplasia and stippling of bone, ophthalmic abnormalities such as optic atrophy, cataracts, and microphthalmia, developmental retardation, seizures, fetal mortality

Note: Data were compiled from the following sources: Lock and Kacew,[1] Roberts,[3] Arena and Drew,[5] Hill and Kleinberg,[6,7] Hill and Stern,[8] Kavlock et al.,[35] Weber,[36] Lane and Hathaway,[37] and Hill and Tennyson.[44] Asterisks denote nonhuman studies.

of potential adverse effects of a drug on the unborn child should be taken into consideration by a physician. Thus, there should be a clear indication that the benefits derived by the mother from a specific drug greatly outweigh the risk to the fetus. Tables 4 and 5 list self-administered drugs (over-the-counter, OTC, preparations) and nontherapeutic drugs (drugs of abuse), respectively. There is, unfortunately, less than adequate awareness of the dangers associated with the use of OTC drugs.

III. DRUGS AND BREAST FEEDING

The nursing mother can serve as a source of neonatal exposure to drugs. No matter whether the agent is an OTC medication or is prescribed by a physician, most drugs are detectable in breast milk. The presence of a drug in maternal milk may be construed as a potential hazard to the infant even though only 1 to 2% of total intake is likely to be found here.[5] Hence, the primary consideration in maternal drug therapy is the risk to the nursing infant rather than the mere presence of a xenobiotic in the milk.

Several factors play a role in determining the quantity of a drug that will be transferred to breast milk. The amount of drug that is actually available for transfer to milk is dependent on certain maternal factors. As outlined in recent reviews,[3,42] the dosage and frequency, as well as route of drug administration, are factors to consider in the mother. Following maternal intake, the pharmacokinetic principles of absorption, distribution, metabolism, and excretion of agent will play a role in determination of drug levels in the milk. The duration of exposure of the infant to lactational drugs can thus vary, depending upon maternal pharmacokinetics. If one considers the infant, the amount and frequency of feeding will affect the concentration of drug ingested. Further, the flow of blood to the breast, the composition of milk, and the rate of milk production, as well as resorption of drug from milk into the maternal circulation, are factors affecting the amount of drug reaching the infant. Finally, the most important factor influencing drug excretion into breast milk is the physicochemical features of the compound.[3,42] The physicochemical characteristics, including degree of ionization, molecular weight, lipid solubility, and protein-binding capacity, will affect the ability to traverse the mammary gland epithelium and thus be available to the suckling infant. It is well established that drug use during lactation will in general result in the presence of these compounds in the milk. As indicated by Roberts,[3] the critical factor to consider during breast feeding is whether the drug utilized poses a documented risk to the infant. From the information available, it is generally believed that few drugs fall into the category of agents which initiate significant and predictable toxicity. Certain drugs should be totally avoided during lactation, and these are shown in Table 6. Drug administration during nursing should be avoided, if possible, or the feeding schedule should be adjusted to minimize chemical levels in the milk. The fact that various drugs are present in breast milk,[5,9] but do not appear to pose a risk to

TABLE 4
Fetal Consequences Attributed to Maternal Ingestion of Over-The-Counter Preparations

Drug	Fetal effect
Acetaminophen	Fetal renal damage, renal failure, congenital cataracts, polyhydramnios
Aloe	Increased intestinal peristalsis, release of meconium *in utero*, kidney damage
Betadine (Povidone-Iodine)	Goiter, hypothyroidism
Caffeine	Neonatal irritability, limb-reduction abnormalities*, low-birth-weight pups*, decreased ossification*, tachycardia
Codeine	Cleft palate and lip, withdrawal symptoms, delayed ossification*
Diphenhydramine	Tremulousness, diarrhea, respiratory depression, withdrawal symptoms
Dextromethorphan	Respiratory depression, withdrawal symptoms
Ephedrine	Fetal tachycardia
Ferrous sulfate	Congenital malformations, GI upset
Hexylresorcinol	Liver toxicity, bone marrow depression, convulsions
Magnesium sulfate	Hypotonia, hyporeflexia, CNS and respiratory depression, decreased adaptation to extrauterine life, convulsions
Magnesium trisilicate	Kidney damage
Phenylpropanolamine	CNS irritability
Pseudoephedrine	Alkalosis
Pyridoxine	Convulsions
Salicylates	GI hemorrhage, neonatal petechiae, cephalohematoma, bleeding tendency, low birth weight, increased perinatal mortality, neonatal pulmonary hypertension
Sodium bicarbonate	Metabolic alkalosis, circulatory overload, edema, congestive heart failure
Theophylline	Tachycardia, vomiting, teratogenesis*
VitaminA	Spontaneous abortion, hydrocephalus, cardiac abnormalities, teratogenesis*, behavioral and learning disabilities*, postnatal growth retardation*
Vitamin D	Supravalvular aortic stenosis, elfin facies, mental retardation, increased fetal death*, skeletal anomalies*
Vitamin K (Menadione)	Jaundice, hematological abnormalities

Note: Data were compiled from the following sources: Lock and Kacew,[1] Roberts,[3] Arena and Drew,[5] Hill and Kleinberg,[6,7] Hill and Stern,[8] Kavlock et al.,[35] Weber,[36] Lane and Hathaway,[37] and Hill and Tennyson.[44] Asterisks denote nonhuman studies.

the infant, should not be deemed to indicate that it is safe to utilize the agent during lactation. A nursing mother should not be discouraged from utilizing drugs if maternal health is at stake. However, excessive use should be cautioned against or alternate, safer therapy should be sought.

IV. DRUGS AND THE CHILD

The pharmacokinetic principles applied in pediatric drug therapy are in general similar to those utilized for adults. However, data obtained in adult studies are not always applicable to rational therapy in infants or young children. The infant must be regarded as a distinct organism. Lack of appreciation of this fact could result in serious harm and potentially result in death. During infancy and childhood, the body weight and composition are continuously changing such that the pharmacodynamic aspects of drug therapy are not predictable. Further, in most cases, the approval of drugs for adult therapy is not accompanied by adequate data to allow for use in children.[10] Despite the informational inadequacies, the utilization of drugs in infants seems to be increasing (Table 7). In their extensive studies, Aranda et al.[11,12] reported that there were more than 30 different preparations which were administered at least once to the neonate. In addition, infants were subjected to polypharmacy as evidenced by at least four different drugs per baby in approximately 50% of the patient population.

TABLE 5
Fetal Effects Due to Maternal Ingestion of Drugs of Abuse

Drug	Fetal effect
Amphetamines	Intrauterine growth retardation, cardiovascular anomalies, biliary tract atresia, prematurity, neonatal lethargy, withdrawal symptoms
Ethanol	Fetal alcohol syndrome, growth deficiency, abnormal facies, CNS disturbances
Cocaine	Mental retardation, motor dysfunction, microcephaly
Heroin	Withdrawal symptoms in neonate, sudden infant death, respiratory CNS depression, thrombocytosis, intrauterine growth retardation, neonatal dependence
Lysergic acid diethylamide	Neurobehavioral abnormalities, teratogenesis*
Marijuana	Neural tube defects*, fetal death*, intrauterine growth retardation*, abnormal neonatal behavior*
Meperidine	Withdrawal symptoms in neonate, sudden infant death, respiratory and CNS depression, thrombocytosis, intrauterine growth retardation, neonatal dependence
Mescaline	Increased resorption rate*, CNS defects*, intrauterine growth retardation*
Methadone	Withdrawal symptoms in neonate, sudden infant death, respiratory and CNS depression, thrombocytosis, intrauterine growth retardation, neonatal dependence
Morphine	Withdrawal symptoms in neonate, sudden infant death, respiratory and CNS depression, thrombocytosis, intrauterine growth retardation, neonatal dependence
Nicotine	Decreased fetal size*, cleft palate*, skeletal anomalies*
Phencyclidine	Abnormal facies, dislocated hip, cerebral palsy

Note: Data were compiled from the following sources: Lock and Kacew,[1] Roberts,[3] Arena and Drew,[5] Hill and Kleinberg,[6,7] Hill and Stern,[8] Kavlock et al.,[35] Weber,[36] Lane and Hathaway,[37] and Hill and Tennyson.[44] Certain categories of drugs which are prescribed are also considered as drugs of abuse, e.g., barbiturates and benzodiazepines. These compounds are presented in Table 3. Asterisks denote nonhuman studies.

Drug utilization and consequent toxicity have also increased among the nonhospitalized pediatric population.[45] Indeed, the prescribing habits of general practitioners were compared to the habits of hospital physicians for the condition of acute gastroenteritis in children. Over a 5-year period, Choonara et al.[41] found that general practitioners prescribed significantly more medicines than did hospital physicians. When one considers that gastroenteritis is self-limiting, this indicates that drug utilization is still too high in nonhospitalized children. Further, Eskola and Poikolainen[13] listed the number of drug poisonings in children aged 0 to 6 years and demonstrated a relationship to the season with recurring peaks over a 3-year period. Various investigators have also reported on a correlation between season and drug poisoning.[14,15] In addition to inadvertent or accidental exposure, failure to comply to the proper use of drugs can either lead to toxicity as a result of excess amount or to ineffective therapy from underdosing.[10] Compliance failure in children can occur when parents are inadequately instructed or where patients refuse to take the drugs as directed. Failure to comply is not restricted solely to the home, but can occur in a hospital.[16-18] It is evident that the pharmacokinetic principles of drug utilization are dependent upon proper pediatric compliance.

A number of important characteristics exist that distinguish drug therapy in infants from adult medication protocols. For example, after intramuscular administration, drug absorption is partially dependent on blood flow in the muscle bed. Abnormal drug absorption following intramuscular injection can occur in premature infants where muscle mass is small and blood flow to the musculature is poor. Examples of adverse effects attributed to altered drug absorption are the reaction of infants to cardiac glycosides and anticonvulsants.[9]

In the infant, absorption from the gastrointestinal (GI) tract of an orally administered drug differs from that in adults. In both adults and infants, the rate and extent of drug

TABLE 6
Drugs in Breast Milk and Potential Adverse Effects

Drug	Consequences
Amantidine	Urinary retention, vomiting, skin rash
Amiodarone	Potential pulmonary toxicity
Amphetamines	Irritability, poor sleeping pattern
Bendroflumethiazide	Suppresses lactation
Bromide	Rash, weakness, absence of cry
Bromocriptine	Suppresses lactation
Cathartics	Abdominal cramping, colic-like syndrome
Chloral hydrate	Sedation
Chloramphenicol	Possible bone marrow suppression, refusal to eat, vomiting
Chlorothiazide	May suppress lactation
Chlorpromazine	Drowsiness, lethargy
Cimetidine	Suppresses gastric acidity in infant, inhibits drug metabolism, CNS stimulation
Clemastine	Drowsiness, irritability, refusal to feed, neck stiffness
Codeine	Bradycardia
Cyclophosphamide	Immune suppression
Diazepam	Sedation, accumulates in infant
Ergotamine	Vomiting, diarrhea, convulsions
Ethanol	Drowsiness, diaphoresis, growth retardation
Gold salts	Rash, inflammation of kidney and liver
Heroin	Neonatal narcotic dependence
Indomethacin	Convulsion
^{131}I	Thyroid suppression
^{125}I	Risk of thyroid cancer
Isoniazid	Pyridoxine deficiency development
Lithium	CNS disturbances, cardiovascular dysfunction
Methadone	Signs of opiate withdrawal if rapidly withdrawn
Methimazole	Decreased thyroid function
Methotrexate	Immune suppression
Metronidazole	Secreted into milk to same level as plasma; thus CNS and hematopoietic adverse effects too risky
Nalidixic acid	Hemolytic anemia
Nicotine (excess)	Shock, restlessness, decreased milk production
Nitrofurantoin	Hemolysis in glucose-6-phosphate dehydrogenase-deficient infant
Oral contraceptives	Breast enlargement, decrease in milk production and protein content
Phenindione	Hemorrhage
Phenobarbital	Sedation, decreased responsiveness, methemoglobinemia, poor sucking reflexes
Phenytoin	Methemoglobinemia
Prednisone	Growth suppression
Salicylates	Metabolic acidosis, rash
Sulfonamides	Increased risk of kernicterus, allergic manifestations
Tetracycline	Possible permanent staining of developing teeth
Tolbutamide	Jaundice

Adapted from Lock and Kacew,[1] Roberts,[3] Arena and Drew,[5] Cohen[9] and Nation and Hotham.[42]

absorption is dependent on the degree of ionization which, in turn, is influenced by pH. Within the first 24 h of life, gastric acidity increases rapidly and this is followed by an elevation in alkalinity over the next 4 to 6 weeks.[3] These conditions result in drugs existing in the infant GI tract in different states of ionization than might be observed in adults. Other factors which modify GI drug absorption in the young infant, as summarized by Roberts,[3] include an irregular neonatal peristalsis, a greater GI tract surface to body ratio, and enhanced intestinal β-glucuronidase activity. The significance of the β-glucuronidase is that it releases drug-bound glucuronide to the free form and thus increases drug bioavailability. The bioavailability of the drug is also related to the diurnal pattern. In general the urinary pH is

TABLE 7
Increased Drug Utilization in Neonates[a]

Drug	% of patients 1974	% of patients 1977
Ampicillin	27.5	42.3
Aquasol	—	10.5
Calcium gluconate	24.7	52.7
Cloxacillin	5.9	10.9
Diazepam	3.8	8.6
Digoxin	6.3	10.5
Furosemide	10.6	24.1
Gentamicin	28.8	43.2
Sodium bicarbonate	22.5	42.7
Phenobarbital	8.8	11.4
Mycostatin	4.7	8.6
Vitamin K	—	25.0

Note: Data were compiled at a neonatal intensive care unit.

[a] Adapted from Aranda et al.[11,12]

acidic during sleep.[19] In infants where the tendency is to sleep for a greater portion of the day, acid drug excretion would decrease in the presence of a low pH, and hence the bioavailability would be enhanced. Krauer[19] demonstrated that the half-life of sulfonamides was increased during the sleep period. In contrast, the bioavailability of basic drugs would be reduced during the sleep phase.

Differences exist in the organ distribution of drugs between newborns and adults. In the newborn, a higher percentage of body weight is represented by water; thus, extracellular water space is proportionately larger.[20] To initiate a receptor response, the distribution of drugs must occur predominantly in the extracellular space; thus, the concentration of drug reaching the receptor sites would be higher in neonates. Further, the ability of newborns to bind drugs in plasma is significantly less than adults.[3,10] This is supported by the findings of Gorodischer et al.[21] who reported a twofold increase in myocardial digoxin levels in infants as compared to adults. Similarly, a fivefold higher myocardium-to-serum ratio was subsequently found in infants administered digoxin in comparison to adults.[29] In addition to digoxin, significantly less plasma protein binding in the infant compared to adult was noted for salicylates, diazoxide, phenytoin, propranolol, phenobarbital, theophylline, penicillin, and lidocaine.[30] As a further complication, drug binding in neonates is also reduced by endogenous substrates including free fatty acids and bilirubin.[22] This again suggests that neonates could be expected to be more susceptible to the effects of free drug circulating in the plasma.

Enhanced susceptibility to adverse reactions in the neonate is a consideration for establishing dosing guidelines on the side of safety. In view of this fact, theophylline was recommended at dose of 6 to 10 μg/ml for the treatment of apnea of prematurity.[38,39] With more extensive study, Gal and Gilman[40] found that a neonate could tolerate a dose as high as 20 μg of theophylline per milliliter of serum, and apneas were eliminated. Based on this growing amount of information, it was suggested that the dosing guidelines and therapeutic range should be reevaluated. This is simply an example of the need to reexamine the current knowledge of pediatric responsiveness to drugs. Thus, acquired data can be used subsequently to establish a more effective therapeutic regimen in the newborn.

Differences also exist with respect to drug-metabolizing enzymes. It has been clearly demonstrated that the drug inactivation rate is generally slower in newborns.[3,23] However, one cannot generalize about the drug-metabolizing capacity in newborns since there is a marked variability among infants and this capacity is highly dependent on the drug being examined.[24] Further, certain metabolic pathways exist uniquely in the neonate.[23,27] Although drug metabolism is a means of chemical inactivation, it is also a process utilized to form an active component. In an effort to obtain a therapeutic effective regimen, this factor must be considered in light of the fact that hepatic drug-metabolizing enzyme capacity is age related. The appreciation of the role of drug metabolism in therapeutics is suggestive that further study is necessary to maximize the ability of the physician to calculate a desired drug dosage.

The ability of the neonate to eliminate drugs via the kidney, the major excretion pathway, is significantly limited by the state of development of these organs. It is well established that the half-life of several antibiotics is prolonged in the neonatal period due to a decreased glomerular filtration rate.[25] However, the glomerular filtration rate reaches the level seen in adults by 5 months of age.[26] In addition, the renal tubular secretory capacity increases during the first few months to attain adult values at 7 months of age.[26] Consequently, an agent eliminated via the secretory renal pathway would have a threefold longer half-life in the infant. Aranda and Stern[28] found that the clearance of phenytoin and phenobarbital was rapid in the first week or two of age, yet theophylline and caffeine clearance remained low until the age of 6 weeks. In a recent study, Leff et al.[34] attributed the need for a greater dosage of phenytoin in infants compared to the adult as a result of increased metabolic clearance in the infant. The knowledge of clearance rates is essential in the consideration of initial as well as subsequent drug dosage in the patient.

V. DRUGS AND THE OLDER CHILD

Within the context of this chapter, the final stage constitutes the older child, where patterns of drug disposition are far less important than dose calculation based on normal growth.[3] As the child grows, the pathways of drug biotransformation and metabolism are similar to that noted in the adult. In addition, the total body water distribution, albeit on a smaller scale, is similar in the child and adult. Despite these recognized similarities, barbiturates produce CNS stimulation in the child as compared to sedation in the adult.[31] Further, cationic amphiphilic drugs such as gentamicin and chlorphentermine are more toxic to the adult than the newborn.[32,33] In a study of 1327 children attending outpatient clinics, the incidence of adverse drug reactions was 0.75%.[43] The nature of these adverse reactions was slight, occurred predominantly in females, and was associated with polypharmacy. As in the case of the neonate, polypharmacy is believed to play an important role in initiation of adverse drug reactions.

There are other problems associated with therapy, the major component being compliance. At this stage of development, the physician is still reliant on an adult, who at the best of times may not be consistent. Ultimately the onus is on the physician to adequately inform the responsible individual of the necessity for compliance and the consequences resulting from failure to adhere.

VI. SUMMARY

The developing organism is unique in its responsiveness to drugs, and the predictability of therapeutic effectiveness based on the adult can lead to grave consequences in the neonate and child. It should be emphasized that adverse drug reactions may take years to become overt, whether the compound is administered to the mother or directly to the child. Although the current trend is geared toward a great use of drugs, the role of the physician should be aimed toward caution rather than overuse. Concurrently with the greater availability of OTC drugs, adequate education of the dangers of these compounds should be promoted. Wiseman et al.[46] recently demonstrated that prescription medications were more frequently involved in accidental poisoning in children compared to OTC drugs. It is of interest that packaging of drugs is now an important consideration in accidental childhood poisoning. The aim of this text is to describe in greater detail the effects of drugs currently and frequently prescribed by the pediatrician.

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Chapter 2

FETAL AND NEONATAL DRUG BIOTRANSFORMATION

Mont R. Juchau

TABLE OF CONTENTS

I. Introduction 16

II. Oxidation Reactions in the Perinatal Period 17

III. Reduction Reactions and Redox Cycling 23

IV. Hydrolytic Reactions 24

V. Conjugation Reactions 25

VI. Summary and Conclusions 29

Acknowledgments 30

References 30

I. INTRODUCTION

One of the most important determinants of drug action is drug biotransformation. Routes and rates of conversion of drugs to various metabolites in the body play a major role (for most drugs) in:

1. Determining the time course and intensity of drug effect
2. Determining the nature, number, time course, and magnitude or intensity of untoward side effects
3. Establishing the ultimate clinical efficacy and usefulness of drugs as therapeutic agents

Publications dealing with the biotransformation of drugs and other foreign organic chemicals of low-molecular-weight (carcinogens, pesticides, steroids, etc.) account for a large share of the literature of pharmacology and toxicology, as well as contributing significantly to several other branches of science. These include the areas of cancer research, mutagenesis, teratogenesis, atherogenesis, molecular biology, endocrinology, lipid research, agricultural chemistry, genetics, and basic biochemistry. This scientific field has become so large that specialization and subspecialization have become the rule. Research on P450 cytochromes alone occupies a very significant percentage of current publications.

The purpose of this chapter is to provide an updated review of drug biotransformation as it applies to the perinatal period. This is a topic that has been reviewed on numerous occasions and with several different emphases. Some of the reviews of this topic that have appeared in the open literature since 1980 are listed.[1-22] For those who are interested in more detailed insights, comprehensive listings of reviews on the subject appearing prior to 1980 are given by Klinger[4] and Pelkonen.[18] No attempt will be made here to be comprehensive. The focus of this review will be on the developmental status of enzymes and enzyme systems that are involved in the catalysis of drug biotransformation reactions during the perinatal period. Emphasis will be placed on the xenobiotic biotransforming P450 isozymes, primarily because the large majority of publications related to this topic which appeared within the past 5 to 7 years have dealt with this group of highly important and extremely interesting isozymes. An increased interest in the role of glutathione and glutathione conjugation has been manifest during the same time period and the pertinent enzymes will also be emphasized. Developmental aspects of glucuronidation have continued to be of interest. However, much slower progress has been evident in recent years for studies of some of the other drug-biotransforming enzymes during the perinatal period and thus will be dealt with only briefly.

Although a seemingly large number of publications dealing with developmental drug biotransformation have appeared, only a few researchers have approached this area in a systematic fashion. Some have focused on prenatal biotransformation in human fetuses; many studies have included only postnatal development in animal models and more recently, investigations have been conducted during the embryonic period. It should be recognized that pharmacokinetic studies have limitations such as

1. They provide a relatively poor view of the biochemistry of the drug-biotransforming enzymes.
2. Suitable animal models for human developmental biotransformation of xenobiotics have not been and are not currently available.
3. Rates and route of drug biotransformation may change very abruptly as a function of age.
4. Predictions of the age-dependent, extrahepatic biotransformation of xenobiotics cannot presently be made on the basis of observations on hepatic metabolism.

It is also clear that observations in one species (or even strain) are not extrapolatable to any

TABLE 1
Perinatal Periods[a] for Various Species

Species	Total gestational time[b]	Perinatal period[c]
Humans	267	67—134
Macaque monkeys	166	42—84
Rats	21—22	5.5—11
Mice	18—20	5—10
Rabbits	31—34	8.5—17
Hamsters	15.5—16	4—8
Guinea pigs	64—68	17—34
Chickens	20—21	5—10

[a] The perinatal period is arbitrarily defined.

[b] Time given in days from Shepard.[26]

[c] Given as the number of days prior to normal parturition (average gestational time) to double that number of days subsequent to normal parturition.

other species (or strain). The rat appears to be a particularly poor model species for studies of developmental drug biotransformation in humans because of its uniqueness in developmental patterns, particularly the sex-dependent developmental patterns occurring postnatally or during the geriatric period.[3] In short, even though much has been published, this area remains poorly developed. Our current capacity to relate drug biotransformational capabilities of the human perinatal organism to drug action in any quantitative sense is woefully inadequate. Even most qualitative predictions are often little more than guesses because of lack of definitive knowledge in the area. Nevertheless, a few generalizations are now possible and some progress has been made. In this review, an attempt will be made to summarize the progress for one relatively specific stage of development — the perinatal period. For convenience and in an effort to be inclusive, this period will be defined arbitrarily as the time extending from the last 25% of the total gestational period (late fetal period) to approximately double that time period following parturition. In humans, this would be from slightly more than 2 months prior to the normal gestational period (approximately 267 d) until approximately 4.5 months subsequent to normal parturition. In rats, the period would extend from roughly day 17 of gestation to 11 d subsequent to normal parturition. For other experimental animals, the period will vary with the total gestational time (Table 1).

The major drug metabolic pathways and their associated enzymes have been discussed in numerous publications, but are presented again here (Table 2) for facility of reference. For many of these pathways and enzymes, only minimal or no progress has been reported in terms of research during the perinatal period.[1-22]

II. OXIDATION REACTIONS IN THE PERINATAL PERIOD

Although drugs may be oxidized via several metabolic pathways (Table 2), the most important pathway quantitatively is via cytochrome P450-dependent monooxygenation. It is now well appreciated that a large number of drug-biotransforming P450 isozymes exists (Table 3) and that each isozyme described to date is subject to different modes of regulation. A considerable amount of confusion in the area of P450 research is attributable to a very large number of laboratory-specific names for the various P450 isozymes. (This has been unavoidable to an extent because one cannot be certain that an isozyme isolated in one laboratory is the same as that isolated in another in the absence of verification of identical amino acid sequences). Recently an attempt has been made to standardize the P450 nomenclature and this is the same nomenclature that will be utilized in the discussions in this

TABLE 2
Common Biotransformation Pathways and Enzymes Involved in Biotransformation

Pathway	Enzymes
I. Oxidation	I. Oxidoreductases
a. Monooxygenation	a-1. Cytochrome P450-dependent systems
	a-2. Flavin-dependent monooxygenases
b. Dioxygenation	b. Dioxygenases
c. Dehydrogenation	c. Dehydrogenases
d. Peroxidation	d. Peroxidases
3. Monoamine oxidation	e. Monoamine oxidases
II. Reductions	II. Oxidoreductases
a. Nitro groups	a. Nitro reductases
b. Azo linkages	b. Azo reductases
c. Epoxides	c. Epoxide reductases
d. Carbonyl groups	d. Dehydrogenases
e. Unsaturated carbon-carbon bonds	
III. Hydrolysis	III. Hydrolases
a. Carboxylic acid esters	a. Esterases
b. Amides/peptides	b. Amidases
c. Sulfate esters	c. Sulfatases
d. Glucuronic acid esters	d. Glucuronidases
e. Epoxides	e. Epoxide hydrolases
IV. Conjugation	IV. Transferases
a. Glycosylation	a. Glycosyl transferases
1. Glucuronidation	1. Glucuronosyl transferases
2. Riboside formation	2. Ribosyl transferases
3. Glucoside formation	3. Glucosyl transferases
b. Sulfation	b. Sulfokinases
c. Acylation	c. Acyltransferases
1. Acetylation	1. Acetyl transferases
2. Glycine/glutamine conjugation	2. Amino acid transferases
d. Glutathione conjugation	d. Glutathione transferases
e. Methylation	e. Methyl transferases

chapter insofar as it is possible (Table 3). Several isozymes have not yet been named in that system, notably g, h, and i (see Table 3). It should be recognized that much of the research has been performed on P450s from rat hepatic microsomal isozymes and, thus, some generalized (but not always warranted) assumptions have been derived by extrapolating from information regarding the rat hepatic isozymes. A more complete listing of P450 isozymes is given by Nebert et al.,[23] but it should be recognized that there is considerable evidence for the existence of many additional P450 isozymes not yet named systematically.

Earlier work on developmental aspects documented that for hepatic tissues in the species studied, total hepatic content of carbon monoxide-binding P450s, as well as several P450-dependent xenobiotic monooxygenating activities, was low during the perinatal period, particularly prenatally and in premature neonates.[1-22] More recent work has tended to focus on development-specific regulation of each of the individual P450 isozymes. Aranda et al.[24] reported that humans at term have total P450 and NADPH-dependent P450 reductase activities that approach approximately one half of the adult values. The relatively recent work of Kitigawa et al.[25] however, illustrates that relative *proportions* of different isozymes can vary dramatically as a function of development. Cresteil et al.[27] postulated that P450s present in late fetal and early neonatal rats were replaced in older animals by immunologically different isozymes, some of them resulting from neonatal imprinting.

Ideally one would wish to have the following information:

1. The number and identity of *individual* P450 isozymes present in hepatic and extrahepatic tissues during the perinatal period

TABLE 3
Nomenclature[a] of Common Hepatic Microsomal P450 Isozymes

Standardized name	Other common names	Inducers[b]
IA1	Rat c, BNF-B; mouse P_1; rabbit 6; human P_1	MC, dioxins, BNF
IA2	Rat d, ISF-G; mouse P_3; rabbit 4; human P_3	ISF, MC, dioxins
IIA1	Rat a, UTF, 3	MC
IIA2	Human 1	
IIB1	Rat b, PBB, PB-4; rabbit 2	PB
IIB2	Rat e, PBD, PB-5	PB
IIC6	Rat k, PB-1, PBC	PB
IIE1	Rat j; mouse ALC; rabbit 3a; human j	Ethanol, isoniazid
IIIA1	Rat p; PCN-E, 2a, PCN1; Rabbit 3c	PCN, DEX
IIIA2	Rat p, PCN2	
IIIA3	Human HLp, nf	
IVA1	Rat LAω, CLO, 452	*Clofibrate*
—	Rat g, RLM-3	
—	Rat h, UTA, 2c, RLM-5, male	
—	Rat i, UTI, 2d, female	

[a] Only a few of the more commonly studied isozymes are presented.

[b] MC, 3-methylcholanthrene; BNF, β-naphthoflavane; PB, phenobarbital; PCN, pregnenolone-16α-carbonitrile; ISF, isosafrole; DEX, dexamethasone.

From Nebert, D. W., Adesnik, M., Coon, M. J., Estabrook, R. W., Gonzalez, F. J., Guengerich, F. P., Gunsalus, I. C., Johnson, E. F., Kemper, B., Levin, W., Phillips, I. R., Sato, R., and Waterman, M. R., *DNA*, 6, 1, 1987. With permission. (For update, see *DNA*, 8, 1, 1989.)

2. A knowledge of the manner in which tissue levels of the individual isozymes fluctuate as a function of age and development during the perinatal period
3. A knowledge of development-dependent as well as development-independent factors capable of regulating levels and activities of P450 isozymes during this period
4. A knowledge of the substrate specificities and kinetic parameters of the individual isozymes and whether these might be altered as a function of development

Data that will ultimately provide answers to these questions are now slowly beginning to emerge.

P450IA1 represents a xenobiotic-biotransforming P450 isozyme for which developmental aspects have probably been studied more extensively (although primarily indirectly) than any other member of the P450 family. It is now presumed that this isozyme does not occur constitutively, at least insofar as has been determined to date. It is strongly inducible by a variety of chemicals of which 3-methylcholanthrene (MC) is the prototype. Several other polynuclear aromatic hydrocarbons (PAH), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and structurally related compounds, β-naphthoflavone (and other flavones), and polyhalogenated biphenyls with planar structures represent those chemicals best known to induce IA1. Indirect evidence derived from studies with these environmentally ubiquitous inducers, as well as with a variety of substrates and inhibitors (including antibodies), suggests that IA1 is inducible in a wide variety of tissues and species and at very early stages of development.[2] For example, several relatively recent studies have shown that enzymes in the preimplantation mouse blastocyst respond to PAH to exhibit a profound increase in capacity to catalyze P450-dependent monooxygenation of benzo(a)pyrene (BaP).[28-30] Although not yet definitively shown, it would seem likely that the induced enzyme(s) would be either P450IA1 or a very closely related isozyme(s). However, because BaP is known to be a substrate for several P450s and because it may be possible that PAHs can induce other closely related P450 isozymes during early stages of development, final judgment must be reserved until more definitive experiments can be performed.

In more recent investigations with rat embryos, fairly conclusive evidence for the presence and functionality of IA1, or a closely related isozyme(s), during very early embryonic development has been provided.[31] Utilizing the following, (1) phenoxazone ethers as probe substrates (2) inhibitory anti-IA1 antibodies and 7,8-benzoflavone as specific inhibitors, and (3) MC as an inducing agent, we showed that the yolk sac as well as the embryo per se appeared to contain functional IA1 (or a very closely related isozyme) after induction. It was considered unlikely that the induced isozyme was IA2 because this isozyme exhibits specificity for catalysis of the *O*-demethylation reaction, in this case, embryonic *O*-demethylation was undetectable even after induction.

In recent attempts to detect messenger RNA for either IA1 or IA2 as a function of early development in rats, it was reported[32] that no message increases for either isozyme could be detected until 6 to 8 d subsequent to parturition. MC was utilized as the inducing agent and sequence-specific, oligomeric deoxynucleotide sequences targeted to IA1 and IA2 mRNAs were utilized as mRNA probes. P450IA1 mRNAs were absent at all ages examined (day 15 of gestation to 40 d of age) in animals not treated with inducing agents. P450IA2 mRNA was first detected constitutively at approximately day 7 postpartum. Both IA1 and IA2 mRNAs were increased by MC pretreatment 1 week postpartum and thereafter, with maximal induction observed at approximately 3 weeks of age. In view of numerous previous studies which have suggested that IA1 is highly inducible at virtually all stages of gestation in several species (including rats), the results were quite surprising but may indicate that MC will induce non-cross-hybridizable mRNA(s) for other developmentally specific P450s.[2,27,31,33-36] These mRNA(s) exhibit substrate specificities, inhibition (with antibodies and α-naphthoflavone), and inducibility similar to that of IA1. Although this may seem unlikely, evidence is accumulating in favor of such a concept. For example, a relatively large body of evidence (albeit mostly indirect) indicates that human placentas of women exposed to PAHs via cigarette smoking contain a highly inducible P450 with characteristics very similar to, if not identical with, those exhibited by hepatic P450 IA1. The evidence, including specific inhibition by monoclonal antibodies directed against IA1, has recently been summarized in a review.[37] The discussion is of importance because, in spite of the many striking similarities, the data suggest that significant differences between the rat hepatic isozyme and the human placental isozyme also appear to exist. A major point discussed was that in spite of extremely profound increases in human placental enzymic activity (including ethoxyresorufin, *O*-dealkylase, and R-warfarin 6- and 8-hydroxylation,[38] reactions regarded as specific markers for IA1), no evidence for a spectral increase or spectral blue shift was apparent in the human tissue preparations.[38] This suggested the possibility of a unique P450 species with an extraordinarily high substrate turnover number that exists in the human placenta (7-ethoxyresorufin is also a substrate for the induced form).[38] It will now be of interest to determine whether increased IA1 mRNA can be detected in the human placenta with hybridization probes after heavy exposure to cigarette smoking. These considerations have several important implications, but the one that should be considered immediately is that a large variety of P450 isozymes may be expressed *only* during prenatal and/or early postnatal life. Additional evidence for this concept of developmentally *specific* biotransforming isozymes has also been discussed more recently by Klinger,[2] Gulyaeva et al.,[39] and Cresteil et al.[27] This concept presents an enormous challenge to investigators in the area because of the very low quantities of P450 isozymes present in prenatal tissues associated with a resultant difficulty in purifying significant quantities of these enzymes for rigorous characterization.

Current concepts regarding the developmental aspects of P450 isozymes inducible by phenobarbital and similar inducing agents seem only slightly more straightforward. Insofar as rat hepatic microsomal P450s are concerned, there are at this writing at least five (and possibly more) hepatic P450 isozymes tht are reportedly inducible by phenobarbital. These include IIB1 (the major phenobarbital-inducible form), IIB2 (97% homologous with IIB1), IIA1 (recently disputed),[40] IIC6 (commonly known as k), and IIIA1 (a major steroid-inducible form often referred to as P450p). Attempts to induce functional P450 isozymes with phenobarbital prenatally have thus far met with success only during the very late stages of gestation.[2] Extensive studies on the mechanism whereby phenobarbital produces an inductive effect have shown that increased rates of transcription of the respective genes (for those thus far investigated) are elicited, but the mechanism whereby gene expression is activated remains an enigma. Unlike MC-type induction discussed above, no receptor for phenobarbital-type induction has yet been identified. Thus, it is not surprising that an understanding of the mechanisms of developmental *control* of phenobarbital-type induction is minimal at present. In relatively recent publications, it was reported that, in uninduced rat liver, IIB2 mRNAs were detectable at birth and concentrations increased as a function of age, suggesting that the IIB2 mRNA is expressed constitutively during the perinatal period.[41,42] The highly homologous IIB1 mRNA (approximately 97% homology), in contrast, did not appear to be expressed constitutively except for a transient expression immediately after parturition. Induction of IIB1 mRNA with phenobarbital was detected only on the last day or two of gestation, in consonance with numerous previous enzymologic investigations regarding the effectiveness of phenobarbital induction during the perinatal period. The induction of IIB1 and IIB2 mRNAs with phenobarbital appeared to be coordinately regulated as early as day 21 of gestation (day prior to normal parturition), but the postnatal constitutive expression of these closely related mRNAs appeared to be regulated independently. The IIB2 mRNA is constitutive in adult rats, whereas the IIB1 mRNA apparently is not. Since prenatal rats were studied only on days 10, 19, 21, and 22 of gestation, it would be of interest to examine time points between days 19 and 21 to determine more exactly the time at which detectable messages begin to be expressed. Also, the extent to which perinatal developmental patterns in rats and other experimental animals compare with patterns observable in humans or nonhuman primates will be of considerable interest. Evidence that phenobarbital-induced mRNA will translate functional hemoprotein during prenatal life is provided by Namkung et al.,[43] who observed threefold increases in rates of aromatic 2-hydroxylation of estradiol-17β catalyzed by fetal hepatic enzymes on days 20 to 21 of gestation. This is a reaction that is catalyzed by a number of P450 isozymes, notably, IA2, IIIA1, and h; thus, the data do not exclude the possibility that prenatal administration of phenobarbital produces increased rates of estrogen 2-hydroxylation via induction of isozymes which are not induced in adult animals. Other investigators demonstrated that P450-dependent monooxygenase activities can be increased by phenobarbital treatment during very late fetal development.

Cresteil[27] also attempted to assess postnatal developmental patterns for six P450 isozymes as well as the effects of MC or phenobarbital as potential inducing agents. The isozymes studied were IA1, IA2, IIB1/2, IIIA1/2, h, and i. The results obtained suggested that none of these (or immunologically cross-reacting) isozymes were detectable in fetal (day 22 gestation) liver unless the dams were treated with inducing agents. Only IIB1/2 appeared in fetal liver after phenobarbital treatment and only IA1 appeared after MC treatment. Only IIB1/2 was detectable constitutively in newborn (12-h post-partum animals), and the effects of inducers were not studied for the same stage of development. By day 5 postpartum, IIB1/2 and h were detectable in the absence of induction, but the other four isozymes were not. Both IA1 and IA2 were detectably inducible by MC at this stage. By day 15 postpartum, only P450i was not detectable constitutively (recognizing that IA1 and IA2 exhibit considerable immunologic cross-reactivity). Monooxygenase activities were detectable at all developmental stages investigated, but the lowest specific activities were detected at the earliest developmental stages.

In preliminary investigations with testosterone as a probe substrate,[111] we found that uninduced rat fetuses near term possessed hepatic enzymes for catalysis of significant rates of hydroxylation at the 15β, 6β, 16α, 16β, and 2β positions on the steroid molecule. Testosterone hydroxylation at the 6β, 16α, and 16β positions can be catalyzed by several P450 isozymes.[44] However, hydroxylation at the 15β and 2β positions suggested a constitutive presence of one or more members of the IIIA family. In addition, treatment of dams with pregnenolone-16α-carbonitrile, a potent inducer of IIIA1, resulted in marked increases in fetal hydroxylation at positions 15β, 6β, 16β, and 2β which is indicative of induction of P450IIIA1 in the fetus. In addition, PCN produced more than 30-fold increases at the 7α position, which suggested steroidal induction of IIA1 or closely related isozyme(s) in the fetal liver.

Recently, Nagata et al.[40] reported that P450IIA1, its associated testosterone 7α-hydroxylase activity, and its mRNA were present at low levels in newborn rats and increased to maximal levels at 1 week of age in both males and females. By 12 weeks of age, the IIA1 isozyme had decreased in male rats but remained elevated in females, providing yet another example of sex-specific P450 isozymes in rats, (g, h, and IIIA2 are male-specific). Other mammalian species have not yet exhibited sex-specific, xenobiotic-oxidizing P450s. In contrast to the reports of previous investigations, Nagata et al.[40] could not demonstrate induction of IIA1 by phenobarbital. MC, however, produced nearly fivefold increases in this isozyme.

Developmental aspects of other P450 isozymes have also been investigated recently, although detailed information during the prenatal and perinatal periods is usually quite limited. Included are studies on P450h (2c),[45,46] P450i (15β),[47] IIIA2(p),[48] IA1(P1),[49] and IA2(P3).[49] The influence of glucocorticoids on the developmental aspects of P450-dependent xenobiotic biotransformation has also been of continuing interest and has been discussed in a number of relatively recent publications.[15,50-54]

It appears that an enormous amount of additional research will be required to provide an accurate picture of the patterns of P450-dependent biotransformation during the perinatal period. A formidable obstacle will be the procurement of reliable data pertaining to humans. Most of the earlier data pertaining to human conceptuses have been obtained from measurements of enzyme activities in fetuses at relatively early stages of gestation (usually 8 to 18 weeks). For the postnatal newborn period, a heavy reliance upon pharmacokinetic analyses has been evident. A major problem with analyses of fetal tissues obtained following spontaneous abortions is the variable but unknown rates of degradation of P450 isozymes, particularly with reference to measurements of enzyme activities.[55] Attempts to deal with whatever is ethically available must, of course, be made, and it may be anticipated that, in the course of time, meaningful statements will be possible.[56-58] At present, the available data from humans suggest that drug-biotransforming P450 isozymes studied to date exist at variably low to negligible levels during fetal life, progressively increase until just prior to parturition, and experience a relatively rapid increase just subsequent or coincidental with parturition, increasing to adult levels at variable rates. A highly interesting and potentially important finding in humans has been the high level of P450-dependent xenobiotic oxidizing activity in the fetal adrenal gland, an organ whose parenchymal cells are largely replaced shortly after birth. Recent investigations with valproic acid as substrate have served to emphasize the high activity (at least for certain substrates) in this organ.[47] Thus far, no other surprises have been encountered and no major deviations from the generalized pattern have been described. Nevertheless, it seems almost inevitable that P450 isozymes that are present only during the prenatal or perinatal stages will ultimately be encountered. Elucidation of their xenobiotic-biotransforming and other functions represents an exciting challenge for the future.

III. REDUCTION REACTIONS AND REDOX CYCLING

Studies of developmental patterns of enzymes that catalyze the reduction of drug/xenobiotic substrates are very rare, and little definitive information can be presented in this review. A recent, speculative review of the potential role of reduction and redox cycling in chemically elicited teratogenesis has been published.[61] However, in terms of the perinatal period per se, we can say only that these reactions are of potential significance. Substrates that are capable of undergoing redox cycling (aromatic nitro compounds, quinones, azo compounds, etc. and chemicals that can be converted to such) are represented among commonly utilized therapeutic agents administered during the perinatal period. Numerous environmentally encountered substances to which the perinatal organism is exposed also fall within this category. A recent series of investigations has demonstrated the potential for prenatal reductive biotransformation (presumably via redox cycling) to elicit profound toxic manifestations in the prenatal target.[62-65] These investigations were performed at a stage of gestation much earlier than the perinatal period, but there seems no reason at present to believe that the same reactions would not occur at later stages of gestation. Peng et al.[66] have recently reported on the capacity of human fetal liver microsomes to catalyze the nitroreduction of clonazepam. The extent to which nitroreduction and/or associated redox cycling may contribute to the deleterious effects of clonazepam, chloramphenicol, or other nitroaromatics in the newborn infant is unknown.[67,68]

Redox cycling has attracted considerable recent attention in consideration of the toxic effects of organic chemicals because the process can evoke cellular and tissue damage by several mechanisms. These include

1. Depletion of cellular reducing equivalents (NADPH, NADH, GSH, etc.)
2. Reduction of tissue oxygen tension, resulting at times in either localized tissue hypoxia, generation of organic radicals with possible subsequent initiation of lipid peroxidation, or other radical-mediated damage
3. Generation of reactive oxygen species, including the highly reactive (and presumably toxic) hydroxyl radical
4. Possibly generation of thiyl radicals

Thus far, most of the interest has centered on compounds bearing aromatic nitro groups (e.g., nitrofurantoin, nitrofurazone, misonidazole, chloramphenicol, clonazepam, etc.) and those bearing quinone/quinonoid structures (menadione, paraquat, adriamycin, mitomycin C, streptonigrin, etc.). It is worthy to note that numerous chemicals can be metabolically converted to metabolites that are potential redox cyclers (e.g., diethylstilbestrol, benzene, etc.). Studies with human fetal tissues have indicated that nitroreduction can be detected in human fetal tissues as early as the seventh to eighth weeks of gestation, but only the fetal liver and fetal adrenal gland were capable of catalyzing conversion to the primary amine in the absence of exogenously added FMN, FAD, or riboflavin.

Evidence for relatively rapid increases in human fetal hepatic and adrenal nitroreductase activities between the 7th and 18th weeks of gestation is available; particularly high and rapidly increasing activities were observed in the fetal adrenal gland. In humans, the fetal adrenal glands are relatively large structures during fetal life, but undergo rapid involution during the first few months of extrauterine life. The high oxidative (*vide supra*) and reductive activities previously exhibited by this gland[7,60] may have important implications for drug toxicity in the perinatal period, but as yet, practical consequences/applications have not been documented to my knowledge. Perhaps a high potential for redox biotransformation somehow contributes to involution of the gland.

Little is yet known concerning the capacity of perinatal tissues to protect/defend against the potential deleterious effects of redox cycling agents. Because redox cyclers are capable of generating reactive oxygen species (e.g., superoxide anions, peroxides, hydroxyl radicals, etc.), it is of interest that recent investigations have further pursued the age-dependence of the level of enzymes that protect against active oxygen species.[69] Levels of catalase, superoxide dismutase, and glutathione peroxidase exhibited varying patterns as a function of age from 3 d before birth to 30 months of age in rat brain. In general, the studies tended to corroborate earlier investigations that focused more specifically on early development.[69-71] It seems likely that future investigations will focus further attention on these aspects as they apply to perinatal development and the effects of chemicals (including drugs) during this developmental period.

IV. HYDROLYTIC REACTIONS

Enzymes that catalyze hydrolytic reactions are referred to as hydrolases. These are enzymes that catalyze reactions in which only the organic substrate and H_2O participate as coreactants where incorporation of H_2O into the substrate often results in cleavage of the molecule. Common xenobiotic substrates are carboxylic acid esters, amides, sulfate esters, glucuronides, and epoxides (Table 2), and a large number of identified drugs and other foreign chemicals exist as (or are readily converted to) these kinds of substances. Except for the epoxide hydrolases, however, little interest in pursuing the developmental regulation of xenobiotic-hydrolyzing hydrolases has been evident in the literature during the past 5 to 7 years. The earlier literature dealing with xenobiotic hydrolysis during the perinatal period was reviewed by Klinger,[2] and it was evident that few unifying concepts could be established at that time. Most of the data were obtained from measurements of enzymatic activities which changed with development in a highly variable fashion, depending on substrate, species, tissue, and probably numerous other factors. Except for the epoxide hydrolases, little has changed in recent years to alter these concepts.

It is now evident that a number of epoxide hydrolase isozymes exist, but at least one of these, a microsomal cholesterol epoxide-hydrolyzing form(s), probably does not participate heavily in xenobiotic biotransformations.[72,73] The cytosolic/mitochondrial form(s) appear(s) to be very active toward *trans*-substituted styrene epoxides, whereas *cis*-substituted epoxides, including epoxides derived from cyclic systems (e.g., benzo(a)pyrene 4,5-oxide), are hydrolyzed almost exclusively by the microsomal (mEH_b) form(s) that act(s) primarily on xenobiotics.[74] Recently, the gene for mEH_b was isolated and characterized.[75] The ontogenetic development of the microsomal, xenobiotic-hydrolyzing form in rat liver occurs beginning with postnatal day 9 and continues for approximately 9 weeks. At postnatal day 6, hepatic activities were very low, but continued to increase until approximately the 42nd postnatal day, and then decreased as a function of age. The decrease was more rapid in males than in females. Earlier work had suggested that the enzyme was present at low levels during prenatal life.[2] Rouet et al.[76] reported that relatively high levels of epoxide hydrolase activity were observable in brain, lung, and liver tissues of perinatal mice. Benzo(a)pyrene 4,5-oxide was used as substrate, and measurements were made at gestational days 17 and 19 as well as at 4, 6, 10, and 20 d of age. Induction with 5,6-benzoflavone was also apparent pre- and postnatally, especially in the lung and liver.

Human fetal livers at gestational ages ranging between 17 and 27 weeks were assayed both immunologically and enzymically with benzo(a)pyrene 4,5-oxide as substrate, and an excellent correlation between the two parameters was found ($r = 0.939$).[55] Epoxide hydrolase activities in fetuses varied from approximately 1 to 3 nmol/mg/min as compared with 7 to 10 nmol/mg/min for corresponding preparations from four adult human hepatic samples.[55] Earlier investigations also indicated that human fetuses possessed relatively high epoxide hydrolase activities.[77] Taken together, the very limited data thus far accumulated suggest that epoxide hydrolases responsible for biotransformation of xenobiotic substrates would exhibit relatively low activities during the *perinatal* period, particularly during the fetal life (or probably in premature offspring). However, these activities in perinatal primates, including humans, would be higher than predicted from investigations in experimental animals such as rats, mice, and guinea pigs. This topic is relatively unexplored, and far more detailed information would be highly desirable, particularly with reference to the cytosolic hydrolase(s) and studies of modes and mechanisms of control during development.

V. CONJUGATION REACTIONS

Some fairly extensive reviews of the literature published prior to 1980 and dealing with developmental aspects of drug conjugation have been provided.[2,78,79] Investigations conducted since the appearance of those reviews have been quite limited with the exception of a relatively large number of studies pertaining to developmental aspects of glucuronidation and the associated transferases, glutathione *S*-transferases, and glutathione conjugation.

Increasing recognition of a multiplicity of glucuronosyl transferase isoforms will necessitate a reevaluation of developmental aspects of xenobiotic glucuronidation with focus on the regulation of development of individual isozymes as they are identified, isolated, purified, and characterized. It has been a rather dogmatic tenet that glucuronidation of xenobiotic aglycone acceptors occurs at extremely low, often undetectable and perhaps negligible rates during prenatal existence, except (in certain species and for certain substrates) at the later stages of gestation. This is normally attributed to a lack of the corresponding glucuronosyl transferase enzymes, but levels of UDPGA and UDPG-dehydrogenase activities are also low in the fetal mammals investigated to date. An important consideration in discussions of ontogeny of the glucuronosyl transferases[80] is the fact that we still do not have complete information regarding enzyme multiplicity. At least seven glucuronosyl transferases are believed to exist (EC 2.4.1.17, 2.4.1.42, 2.4.1.59, 2.4.1.61, 2.4.1.76, 2.4.1.77, and 2.4.1.95), but still others are thought to exist based on more indirect but fairly convincing evidence. Of these, only 2.4.1.17 is believed to participate extensively in xenobiotic glucuronidation, but there appear to be at least two subclasses of EC 2.4.1.17 These two have been classified at least partially on the basis of ontogenetic considerations in studies with rats. They have been designated as Group 1 and Group 2 glucuronosyl transferases from observations in rodent species. The glucuronosyl transferase(s) designated as Group 1 has the following characteristics:

1. They exhibit a substrate specificity for aglycones that tend to be relatively small and planar (e.g., *o*-aminophenol, *p*-nitrophenol, α-naphthol, etc.)
2. They are inducible by 3-methylcholanthrene
3. They are activated preferentially by phospholipase A
4. They tend to exhibit localization in the rough endoplasmic reticulum
5. They are distributed relatively ubiquitously in most mammalian tissues, but seem to be deficient in cats, fish, and Gunn rats.

Important from the point of view of this review is the exhibition of a late fetal development in rats, but not in humans. In the rat, transferase levels become detectable at about day 16 of gestation, reach a maximum just prior to or at birth, and then decline after parturition. Experimentally, treatment of rodents with certain glucocorticoids can trigger a precocious development.

This is contrasted with Group 2 glucuronosyl transferase(s) which

1. Exhibit inducibility by phenobarbital

2. Are preferentially activated by trypsin
3. Are localized predominantly in the smooth endoplasmic reticulum
4. Are present predominantly in the liver and intestine

Larger and relatively nonplanar substrates are preferred as aglycone acceptors (e.g., morphine, chloramphenicol, etc.), and a "neonatal" developmental pattern is observed in which activities are normally first detectable subsequent to parturition. Glucocorticoids do not elicit precocious developmental patterns. Whether the Group 1 or Group 2 transferases may be further subdivided is open to question at present, but accumulating evidence would seem to suggest that additional subdivisions may be appropriate. Certainly insofar as endogenous steroid aglycone acceptors are concerned, glucuronosyl transferases other than EC 2.4.1.17 are functional, and xenobiotic steroids would probably be expected to utilize those transferases in the catalysis of their glucuronidation. Most of the steroid transferases exhibit a "neonatal" pattern of development.

Also of importance are the relatively profound species differences that exist in terms of developmental patterns. In humans, for example, the xenobiotic glucuronidating transferases all (with possible exceptions, *vide infra)* seem to appear postnatally. Thus, the fetus and premature newborn would be expected to have extremely low to negligible levels of virtually all glucuronosyl transferases identified to date. Also, human glucuronidation capacity in general would be expected to be severely compromised immediately after parturition, even in full-term infants, and would then increase and reach adult levels within a few months. Little has been written that would tend to contradict these expectations. Compromised glucuronidation capacity probably represents one of the most important factors which may account for the (generally) increased susceptibility of perinatal organisms to the toxic effects of drugs and other environmental chemicals.

Some recent investigations in sheep have suggested, on the basis of studies of kinetic parameters and effects of allosteric effectors, that fetal glucuronosyl transferase isozymes may differ from adult isozymes.[81] These ideas need to be pursued further, but this will be extremely difficult because of the membrane-bound nature of the enzymes and their striking dependence on specific phospholipid environments.[82] In recent studies with post-mortem samples of human liver, it was reported that glucuronosyl transferase activities using bilirubin, androsterone, testosterone, α-naphthol, *p*-nitrophenol, and *o*-aminophenol as substrates were present in fetal and term liver samples at less than 14% of adult values.[83] In contrast, however, fetal and neonatal glucuronidation of 5-hydroxytryptamine occurred at 109 to 121% of adult values. The authors suggested that a human fetal 5-hydroxytryptamine-glucuronidating transferase may exist in human liver that is more restricted in substrate specificity compared to those of the rat or rhesus monkey. If confirmed, this would represent a striking exception to the previously held notion that *all* human glucuronosyl transferases are extremely low at birth. It is also of interest that the rhesus monkey appeared to be more similar to the rat than to humans in terms of the observed developmental pattern. With morphine as aglycone acceptor, Pacifici et al.[84] reported glucuronidation rates in human fetal livers that were one tenth to one sixth those observed in adults, with no correlation between activity and gestational age (15 to 27 weeks). However, this may be one of the only xenobiotic aglycones for which such relatively high activity can be detected in human fetal livers.

A highly interesting recent observation was made by Harris and Bradshaw,[85] who observed that prenatal exposure to a "methylcholanthrene-type" inducing agent (3,4,3′,4′-tetrachlorobiphenyl) on days 6 to 18 of gestation would produce a relatively long-lasting increase in glucuronosyl transferase activity. In treated litters, 3-week-old offspring exhibited activities with *p*-nitrophenol as substrate that were threefold higher than those measured in the corresponding controls.

Particularly encouraging in recent years has been the progress in isolating and purifying specific glucuronosyl transferase isozymes[86-89] and in investigations of the molecular biology of these important enzymes.[90] These kinds of advances promise to help clarify a great many questions pertaining to developmental aspects of glucuronidation.

Sulfation has long been regarded as a high-affinity, low-capacity "back-up" conjugation reaction for glucuronidations with the implication that sulfation assumes an important functional role for cases in which glucuronidation processes are inhibited or are otherwise inadequate for conjugation of phenols (primarily) or other acceptor molecules (e.g., alcohols, amines, catechols, oximes, amides, etc.). In recent years, this concept has also attracted attention in consideration of acetaminophen hepatotoxicity in adults. The concept is particularly attractive for discussion of developmental aspects because of the relatively well-established glucuronidating deficiencies that exist during the perinatal period (*vide supra*). Factors determining the ratios of glucuronidation/sulfation for particular situations have been discussed by Mulder.[91]

The degree to which the concept may be applicable to developmental processes has not been examined in a rigorous, systematic fashion, and this area of research is clouded by uncertainties regarding factors such as (1) species and strain differences, (2) the relative importance of the various enzymes and cofactors involved in sulfation reactions under given sets of conditions (the availability of inorganic sulfate often represents the limiting factor in rates of sulfation), and (3) the relative participation of a fairly large number of identified and possibly unidentified sulfotransferase enzymes. It now seems apparent that at least four forms of the major xenobiotic sulfating enzyme EC 2.8.2.1 exist.[92] However, unlike most other xenobiotic-biotransforming reactions, a thorough understanding of the catalyzing enzyme(s) assumes a more secondary role for sulfation processes. Factors regulating the pertinent tissue levels of inorganic sulfate are often more meaningful than sulfotransferase levels when extrapolating to sulfation rates *in vivo*. For this reason, studies such as those reported by Cole et al.[93] are particularly pertinent to the developmental aspects of drug sulfation, even though serum rather than tissue levels of inorganic sulfate were measured. These investigators reported a significant maternal-fetal serum sulfate gradient in favor of the fetus and suggested that the gradient was actively generated across the brush border of the placental syncytiotrophoblast. This, in turn, suggests that the placenta may play a critical role in determining rates of fetal sulfation of drugs.

It should be recognized that, at present, only extremely limited and fragmentary data (which often appear conflicting) are available concerning perinatal drug sulfation. It would seem that the time is now ripe for a thorough investigation of perinatal xenobiotic sulfating capacity and regulation thereof. In view of the complexity of the entire sulfation process, the potentially large number of factors capable of participating in sulfation regulation, and the probability of profound species/strain differences, this would appear to be a formidable task. However, the increase in overall understanding of sulfation processes, the availability of the necessary technology, and the importance of the needed information all argue strongly in favor of initiation of a fresh approach toward an understanding of developmental aspects of xenobiotic sulfation.

Gluthathione (GSH) and GSH transferases (EC 2.4.1.18) play extremely important roles both in the cellular economy and in protecting cells against the deleterious effects of reactive electrophilic intermediary metabolites of xenobiotics, such as epoxides, hydroperoxides, and activated alkenes. GSH, a soft nucleophile, will covalently bind quite readily to soft electrophiles, even in the absence of catalyzing transferases, and will thus inhibit the covalent binding of such soft electrophiles to important cellular macromolecules with soft nucleophilic centers, e.g., proteins bearing sulfhydryl residues. Conjugation of GSH with macromolecules bearing hard nucleophilic centers (e.g., nucleic acids), however, appears to proceed at slow to negligible rates in the absence of appropriate GSH transferases. Details of these ideas

TABLE 4
Cytosolic Rat Hepatic GSH-Transferases

Nomenclature[98]	**Older names**	**Peroxidase activity**	**Dimer mol wt (daltons)**
1-1	Ligandin, B_1, Y_aY_a, L_2, B	High	51,000
1-2	Ligandin, B_2, Y_aY_c, BL, B	High	53,000
2-2	AA, Y_cY_c, B_2	High	56,000
3-3	A, $Y_b{}^1Y_b{}^1$, A_2	Negligible	53,000
3-4	C, $Y_b{}^2Y_b{}^2$, AC	Negligible	53,500
4-4	D, $Y_b{}^2Y_b{}^2$, C_2	Negligible	54,000
5-5	E	High	58,000
6-6	M_T	High	52,000
7-7[a]	P, Y_pY_p	High	48,000
8-8	Acidic GSH-transferase	?	49,000

Subunit	**Substrate preferences**	**Monomer mol wt (daltons)**	**Inducers**[b]
1	Androstenedione, BSP	25,600	PB, MC, PTU
2	Ethacrynic aid, glycidoxycoumarin	28,000	—
3	BP-oxide	26,500	PB and MC
4		27,000	?
5	Glycidoxycoumarin, BP-oxide, CDNB	29,000	?
6		26,000	?
7[a]	Ethacrynic acid	24,000	?
8	4-Hydroxyalk-2-enals, ethacrynic acid	24,500	?

Note: Criteria for classification of transferase subunits:

1. Substrate preferences/binding specificity
2. Molecular weights
3. Immunologic cross-reactivity (only 3 and 4 cross-react)
4. Peroxidase activity (2 > 1 > 5, 6, 7 >>> 3, 4)
5. Isoelectric points (shown in descending order)
6. Elution from CM52 columns

[a] Not present in normal liver; present in hepatic tumors. In addition, at least one membrane-bound (microsomal) transferase[99] has been identified in rat liver.

[b] PB, phenobarbital; MC, 3-methylcholanthrene; PTU, propylthiouracil.

have been discussed by Coles.[94] Thus, the transferases appear to be of particular importance in protecting against the genotoxic effects produced by harder electrophiles.

The GSH transferases comprise a large family of enzymes, the numerous members of which are currently being discovered at a rapid rate. These enzymes exist as various combinations of dimeric subunits, as is depicted in Table 4. As an example of multiplicity, recent results of studies of GSH transferases in rat brain indicated that even though a close relationship with the hepatic enzymes appeared to exist, the brain enzymes exhibited unique features not observed among the transferases of other tissues.[95] These observations indicated that each tissue may possess its own complement of unique, tissue and species/strain-specific isoforms.[96] This further suggests that a variety of unique isoenzymes may be expressed at various periods during the course of development.[97]

Guthenberg et al.[100] recently isolated two distinct forms of GSH transferase from human fetal liver that exhibited some similarities to adult forms, except that the fetal enzymes appeared to be considerably more efficient in terms of catalytic activity with styrene 7,8-oxide as substrate. It will be of interest to determine whether the human fetal liver has subunits not present in livers of human adults. However, it was recently reported that 13 forms of glutathione *S*-transferase could be isolated from livers of humans of varying age and sex.[101] Thus, considerable effort will be required simply to determine *whether* different developmental stage-specific isoforms exist (much less how many differences), and a characterization of the developmental pattern of each isoenzyme will be necessary.

Most studies indicate that prenatal hepatic glutathione *S*-transferase *activities* are low to nondetectable prenatally and in newborns (for most substrates), but then exhibit increases which vary with species, strain, tissue, sex, and substrate.[76,102-108] An exception to this appears to exist in humans in which relatively high activities have been measured prenatally.[79] These observations are in agreement with those reported in earlier reviews on the subject.[2,78] Important facets remaining to be investigated with reference to the perinatal period include

1. The identification of isozyme complement in both hepatic and extrahepatic tissues
2. The change in complement measured as a function of age during the perinatal period
3. A knowledge of the substrate specificity and kinetics of the isozymes that are present during this period
4. Modes/mechanisms of regulation of levels and activities of each of the isozymes

In addition, further studies of ontogenic changes in levels and disposition of GSH per se (and regulation of such changes), as exemplified by the recent studies of Taniguchi and Inoue,[109] would be highly desirable. Finally, it would be of importance to investigate the degree to which perinatal GSH transferases would exhibit the potential to participate in bioactivating reactions. This would be of special interest and importance from a toxicological point of view.[110]

Investigations of perinatal aspects of xenobiotic acylation reactions (amino acid conjugations and acetylation reactions) and of other conjugation reactions listed in Table 2 have been extremely rare since the publication of previous reviews of these topics.[2,78] Further consideration in this review does not appear to be warranted.

VI. SUMMARY AND CONCLUSIONS

Progress in understanding the developmental aspects of xenobiotic biotransformation during the perinatal period has been relatively slow, but several important generalizations have emerged that appear to merit a reiteration:

1. Due to the potentially rapid changes that may accompany development in the genetic expression of xenobiotic biotransforming isozymes, extrapolations from one stage of development to another (even within a relatively short time frame) may be invalid.
2. Extrapolations from species, even among relatively closely related species (e.g., rhesus monkeys to humans, rats to mice, etc.), are clearly unwarranted. In discussions, species, strain, and stage of development should be clearly stated.
3. Measurements of enzymatic activities with particular substrates normally have very limited value in determining the overall metabolic capabilities of developing tissues. This has been greatly emphasized in recent years with the increasing number of isozymes for virtually all classes of xenobiotic biotransforming enzymes.
4. In addition to stage-specific isozymes, it is increasingly clear that tissue-specific isozymes exist and that measurements in hepatic tissues need not apply to extrahepatic tissues or vice versa.
5. Modes and mechanisms of *regulation* of each isozyme may be isozyme-specific and will probably vary with age, species, strain, and specific tissue.

6. The most usual scenario for drug-biotransforming enzymes during the perinatal period is the presence of low/negligible quantities in hepatic tissues. The number of exceptions to this generalization is sufficiently high to preclude sweeping generalizations. This is particularly true in humans.
7. When bioactivating reactions are involved, extremely low activities may be sufficient to elicit profound toxicity.
8. Few if any sex differences in xenobiotic biotransforming isozymes have been documented during the perinatal period.
9. Very little information is currently available concerning xenobiotic biotransformation in extrahepatic tissues during the perinatal period. It may be that certain extrahepatic tissues (e.g., human fetal adrenal gland) are highly endowed with certain isozymes that catalyze xenobiotic biotransforming reactions.

10 Age-dependent changes in drug biotransformation frequently appear most rapid during the perinatal period. Rates of changes are often most rapid immediately after parturition.

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Chapter 3

EFFECTS OF CISPLATIN ON THE CHICK EMBRYO — A MODEL FOR THE ANALYSIS OF PRENATAL TOXICITY

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TABLE OF CONTENTS

I. Introduction 36

II. Prenatal Life Periods 36
  A. Insensitivity Period 36
  B. Period of Teratogenicity 36
  C. Period of Fetal Toxicity 37

III. Antineoplastic Agents as Teratogens 37

IV. Cisplatin 38
  A. Chemical Nature and Mechanism of Action 38
  B. Adverse Effects in the Chick Embryo 38
    1. Microphthalmia 38
    2. Brain Necrosis 40

V. General Considerations 41
  A. Mechanisms Involved in Microphthalmia 41
  B. Mechanisms Involved in Prenatal Brain Lesions 43

VI. Summary 45

Acknowledgments 46

References 46

I. INTRODUCTION

The effects of a given toxic substance, when administered during the prenatal period, generally include lesions which are typical of the response of the adult organism to that same toxic substance and, in addition, changes which are characteristic of the stage of development at which the substance is administered. In this chapter I shall discuss mainly those responses which are typical of the developmental period. The effects of toxic agents during prenatal life vary according to the stage at which they are administered. In this respect we might divide prenatal life into three periods: insensitivity period, period of embryonic teratogenicity, and period of fetal toxicity.

II. PRENATAL LIFE PERIODS

A. INSENSITIVITY PERIOD

During this period, toxic agents fail in general to produce malformations: large doses might kill the embryos, and lower doses, which do not kill them, leave embryos unaffected. The reason for this lack of response of early embryos is not understood. It is possible that lesions at this stage might be produced, but be reversible.[1] It has been shown that if one mechanically separates or destroys several of the cells of an embryo at the stage of morula, the remaining cells may still be able to complete normal development. One can postulate that this process, known as *regulation*, might also occur after the destruction of few of the cells of a blastocyst by a toxic agent.[1] In most species, the period of insensitivity to teratogenic stimuli ends approximately at the time of neurulation. Neurulation (formation of the neural plate and neural groove) occurs in the human in the third week of development[2] and occurs in the rat on the seventh day of development.[3] The chick embryo starts to develop before the egg is laid and neurulation occurs during the first day of incubation.[4]

B. PERIOD OF TERATOGENICITY

Neurulation inaugurates a period of very active morphogenesis in which most of the organs and structures acquire their shape and basic organization. It is during this period precisely that toxic agents produce the most common types of malformations and are thus considered as "teratogens". In the case of the human embryo, this period lasts until the 11th or 12th week of development.[2] In the case of the rat embryo, it extends between the 7th and 19th days.[1] and in the chick embryo it lasts until approximately the 9th day. Not all organs and structures develop simultaneously, and each one of them has a relatively short "susceptible" period during which it is more amenable to toxic lesions.

There are several peculiarities in the teratogenic response that have been well known for many years. Thus, Stockard[5] suggested four principles governing causation of malformations as follows:

1. Every type of developmental monster known in the literature may be produced by one and the same experimental treatment.
2. The same structural abnormality may be induced in the embryos of various species by a great number of different experimental treatments.
3. In all cases, the initial effect of the experimental treatment is a lowering of the developmental rate, and the resulting deformity is always secondarily due to this slow rate of development.
4. The type of monster or deformity is determined by the developmental period during which the slowing in rate is experienced.

Stockard's principles[5] are accepted, with few modifications, by most teratologists. These principles assume the lack of specificity in the response of embryos to different teratogenic stimuli. The reason for this lack of specificty appears to reside in the fact that during the early embryonic period, teratogens are acting on undifferentiated or slightly differentiated cells. Microphthalmia is a relatively frequent and typical teratogenic response and will be used as a model to illustrate the characteristics of a response to toxic substances during the embryonic period.

C. PERIOD OF FETAL TOXICITY

Upon reaching the fetal stage, the embryo has acquired the external shape and internal organization which are characteristic of its own species. The most important morphogenetic processes, such as the formation of the face, the closure of the palate, the septation of the heart, the formation of the diaphragm, etc., have all been completed. From now on, the fetus will continue to grow at a slower pace and its cells will be acquiring functional differentiation. For this reason, toxic agents will tend to produce lesions similar to those induced in the adult organism (fetal toxicity) rather than the malformations seen during the embryonic period (teratogenicity). There are exceptions to this generalization, and the main one is represented by the brain. This organ continues to grow and change shape and structure during the fetal period; in the case of the mammal, the process continues until or beyond birth. For this reason, malformations of the brain can also be produced during the late stages in development. The lesions produced by cisplatin in the brain of the chick embryo will be described in detail and used as an example of a malformation induced at an age in which malformations of most other organs are not usually produced.

III. ANTINEOPLASTIC AGENTS AS TERATOGENS

During the last 30 years, successful treatment of various malignant tumors has been achieved through the administration of various substances which can be grouped under the name of antineoplastic drugs. Antineoplastic agents have been variously classified in overlapping categories according to their chemical composition or to their mechanism of action (alkylating agents, antimetabolites, antimitotic alkaloids, etc.). Despite their variable chemical composition, they all have in common the property of inhibiting the mitotic process, killing dividing cells at different stages of the mitotic cycle, and/or killing nonmitotic cells during early stages of their differentiation.

Cell proliferation and cell differentiation are key processes in embryonic development, and almost all antiproliferative agents administered during the embryonic or fetal periods produce malformations or tissue damage. Being aware of this, physicians avoid prescribing antiproliferative agents to pregnant women unless absolutely required. There are isolated reports of cases in which antineoplastic agents administered during pregnancy induced serious fetal malformations, but there are also few in which the administration of these agents was followed by the delivery of a normal baby.[6] The different outcome must be interpreted in terms of differences in doses, length of treatment, and/or stage of pregnancy during which the treatment was conducted.

The interest of teratologists and toxicologists in research involving the use of antineoplastic drugs during development has not been directed in general toward trying to find effective antineoplastic drugs which could be used safely during pregnancy, but rather to obtain information on (1) mechanisms of normal and abnormal morphogenesis of particular organs and (2) mechanisms of action of the drugs themselves. Occasionally, embryos have been used in order to scan potential antineoplastic agents.[7]

The results of our experiments using cisplatin on the chick embryo illustrate well the type of information obtained in experiments with antineoplastic agents in general. The injection of cisplatin to the chick embryo produces various types of changes, including hepatic lesions and destruction of germ cells. I shall focus, however, on the two best-studied lesions: brain necrosis and microphthalmia.

IV. CISPLATIN

A. CHEMICAL NATURE AND MECHANISM OF ACTION

There are excellent reviews discussing in detail the chemical structure and mechanisms of action of cisplatin.[8-11] It will suffice here to make a brief description of the existing knowledge in this respect. Cisplatin (*cis*-dichlorodiammineplatinum II) belongs to a family of coordination complexes of platinum. Thus, different from most antineoplastic agents in current use, cisplatin is an inorganic substance. In its molecule one atom of platinum is bound to two chloride atoms and two ammonia groups. The *cis* configuration appears to be important for the determination of its properties since coordination complexes with *trans* configuration are devoid of antineoplastic activity.[8] It is the dissociation of the chloride atoms from the complex which appears to facilitate the binding of the complex to various groups, and this probably constitutes the basis for its best-known property, namely, that of producing inter- and intrastrand cross-linking of DNA.[9]

As a result of the above-described properties, cisplatin has been shown to inhibit DNA synthesis, inhibit mitosis, produce mutations, and selectively kill dividing and immature cells. This selectivity is not complete, and some fully differentiated nonactively dividing cells can also be affected. Of special importance for the clinical use of the compound is the fact that kidney tubular epithelial cells are frequently affected. Due to the similarity of the kidney lesions to those produced by other metals, such as mercury, it has been suggested that the cytotoxic effects of cisplatin might be due not to the alkylating properties of the whole molecule, but rather to the action of metallic platinum itself. Thus, when studying the action of cisplatin on embryonic cells, one should try to establish which of these two possible mechanisms is responsible for the cytotoxicity observed.

Cisplatin has not been previously administered to chick embryos. It has been shown, however, to produce fetal resorptions and skeletal malformations in mice and rats.[12,13] Köpf-Maier and Merker[14] found that cisplatin produces necrosis of the neocortex in rat embryos, but indicated in a subsequent paper that no major malformations, apart from brain damage, could be detected.

At the beginning of our study using the chick embryo, we concentrated our attention on the possible effects of cisplatin on the embryonic kidneys (mesonephros and metanephros), but we failed to find changes in these organs. However, we found that when injected at early ages (4 to 6 d of incubation), cisplatin produced microphthalmia with great frequency, and that when injected at later stages (10 to 11 d), brain necrosis, liver damage, and destruction of the germ cell line were produced. In this chapter we shall only discuss the changes observed in the eye and the nervous system.

B. ADVERSE EFFECTS IN THE CHICK EMBRYO

1. Microphthalmia

A detailed account of the experiments in which we succeeded in producing microphthalmia through the injection of a single dose of cisplatin has been published.[15] For this reason, we shall only summarize the main findings.

Eggs from white Leghorn hens obtained from a commercial source were incubated in a forced-draft incubator at 37°C and 60% relative humidity. Platinol was kindly supplied by Bristol Laboratories (unit of Bristol-Meyers Canada, Inc., Belleville, Ontario, Canada). This pharmaceutical product consists of a solution containing 10 mg of cisplatin, 90 mg of sodium chloride, and 100 mg of mannitol in 10 ml of distilled water. Further dilutions were made using saline. Doses ranging between 10 and 100 ng of cisplatin dissolved in a total

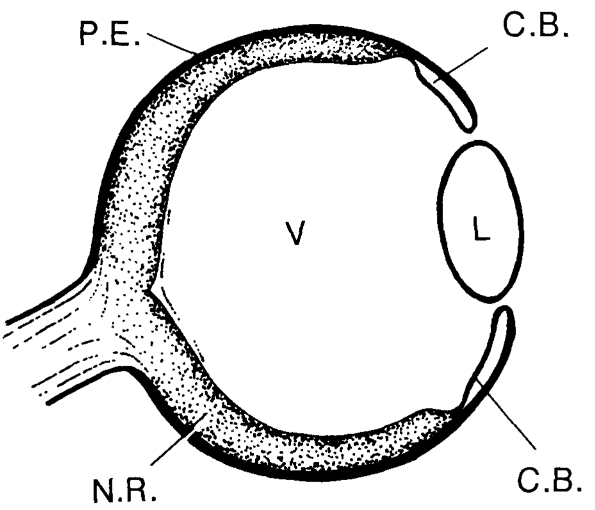

FIGURE 1. Schematic representation of the eye from a 5-d-old chick embryo. The outer layer of the optic cup has transformed into the pigmented epithelium (P.E.) and the inner layer, now stratified, constitutes the neural retina (N.R.). In the outer portion of the cup, both layers remain thin and will form the epithelium covering the ciliary body (C.B.); L, lens; V, vitreum.

volume of 0.1 ml were injected into the air chamber of each egg. In all experiments, controls consisted of uninjected embryos and embryos injected with a solution containing the same concentration of sodium chloride and mannitol as the one used in experimental embryos, but in which cisplatin had been omitted. Doses and treatment schedules were selected after preliminary experiments.

Bilateral micropthalmia appeared in 88% of the surviving embryos injected on the fifth day with 75 ng of cisplatin. The injection of 100 ng produced a higher frequency of microphthalmia, but also very high mortality. Doses as low as 25 ng per egg produced mild microphthalmia in 28% of the injected embryos. The reduction in size of the eyes in the treated embryos, as judged by comparison with the corresponding controls through a dissecting microscope, became evident 3 d after the injection. No other malformation was observed in this experimental group.

A detailed study was conducted on the inner structure of the eyes from embryos injected with 75 ng and sacrificed at various intervals after the injection. When bisected eyes were observed with a dissecting microscope, it became evident that all microphthalmic eyes had lesions of the ciliary zone. Ciliary processes, which were evident in the controls, were not seen in the affected eyes, and the distribution of the pigment in this zone was irregular. These alterations became evident 2 to 3 d after the injection and progressed rapidly. When examined 6 d after the injection, the ciliary zone could be distinguished only with difficulty, and the retina presented large folds which occupied almost the whole cavity of the eye. These results are illustrated in Figures 1 and 2. Figure 1 shows the eye on the fifth day of incubation. The peripheral part of the optic cup, i.e., the part closer to the lens, constitutes the primordium of the ciliary body, and the rest forms the retina which consists of the outer pigmented epithelium and the inner, stratified neural layer. Figure 2 illustrates the organization of the microphthalmic eye as seen 6 d after the injection; although the eye has failed to expand in size to the same extent as the controls, the neural layer of the retina continued to grow and became folded upon itself in order to accommodate to the space available.

The histological study showed that degenerative lesions were present in the ciliary epithelium as early as 3 d after the injection. The cells of this ciliary epithelium presented

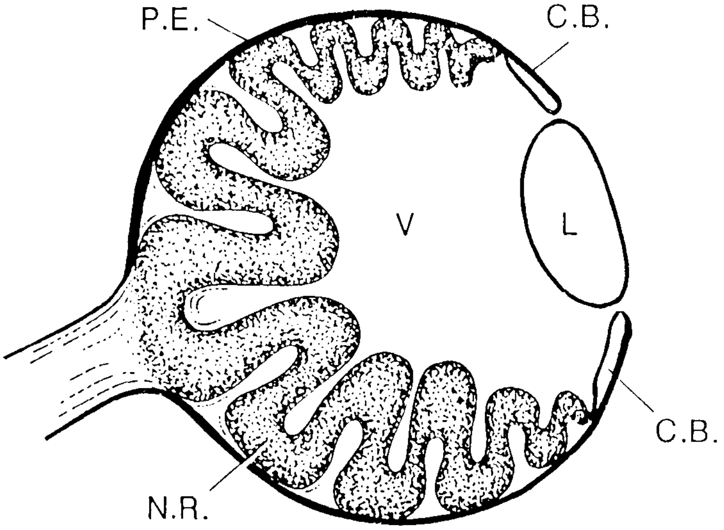

FIGURE 2. Schematic representation of experimental microphthalmia in a chick embryo. The eye has failed to grow as a whole, but the neural retina (N.R.) has continued to grow and fold upon itself; C.B., ciliary body; L, lens; P.E., pigmented epithelium; V, vitreum.

large cytoplasmic dark inclusions. When observed with the electron microscope, these dark bodies were shown to be dense bodies, probably of lysosomal nature. By the sixth day after the injection, the inner layer of the ciliary epithelium was totally degenerated.

Contrary to what happened to the ciliary epithelium, only a very small proportion of the cells in the neural layer of the retina presented degenerative changes. Although no precise determination of the mitotic rates was conducted, subjective appreciation of mitotic activity of the basal cells in the neural epithelium of the retina did not show clear differences between microphthalmic and control eyes. This fact agreed well with the interpretation that the neural epithelium had continued to grow in spite of the lack of expansion of the eye as a whole and was thus forced to fold in order to accommodate to the space available.

2. Brain Necrosis

Brain lesions were produced by a single dose of cisplatin administered between the 8th and 12th day of incubation; these lesions appeared with higher frequency when the injections were made on the 11th day. At this age, the dose required to produce lesions ranged from 50 to 200 ng per embryo.

The lesions were detected by inspection under a dissecting microscope; the most serious ones consisted of necrosis of the whole brain, which became transformed into a soft, dark, hemorrhagic mass and could not be dissected without becoming disintegrated. Most commonly, lesions were limited to smaller, symmetrically arranged zones. These localized lesions were recognized because of their somewhat darker color or, less frequently, because of the presence of a large number of punctiform hemorrhagic foci.

When embryos were injected on the 11th day with 100 ng and examined on the 17th day, lesions were found in 77% of the cases; in most of the cases, these lesions were of the localized type. They were found most frequently in the caudal part of the cerebral hemispheres. The optic lobes were affected somewhat less frequently and changes were never observed in the cerebellum. The dose of 200 ng produced massive brain necrosis in 60% of the embryos. Mild brain lesions were induced by doses as low as 25 ng.

When embryos receiving 100 ng of cisplatin on the 11th day were kept in the incubator for 11 additional days only 35% of the embryos succeeded to hatch. Some of those which hatched were unable to stand or feed themselves. When killed and dissected, it was found that these chicks had extensive brain lesions. Surprisingly, even those which hatched and appeared completely normal also had more or less severe lesions almost always restricted to the cerebrum.

Plate 1A* illustrates the histological characteristics of the fully developed necrotic changes. It is a micrograph from a cross-section of the telencephalon from an embryo sacrificed 6 d after the injection of 200 ng. Most of the tissue has degenerated, and the necrotic central part of the corpus striatum, which was completely liquefied, disappeared during histological processing.

In order to analyze the evolution of the lesions, histological and electron microscopical studies were conducted on the caudal zone of the cerebral hemispheres of embryos injected on the 11th day with 100 ng cisplatin and killed at daily intervals. Few of the embryos presented small hemorrhagic foci 1 d after the injection, as shown in Plate 1B; in almost all zones, whether there were hemorrhages or not, numerous neurons could be found which contained cytoplasmic inclusions which stained intensely with toluidine blue (Plate 1C). The zones where hemorrhages had occurred contained numerous vacuolized macrophagic cells 1 and 3 d after the injection (Plate 1D); in the zones devoid of hemorrhagic foci, the only change observed consisted in an increase in number and size of the previously described dark bodies. The electron microscopical observations showed that the dark bodies observed with the light microscope corresponded to dense bodies, probably of lysosomal nature (Plate 2A). Although occasionally dense bodies could be found in the perikaria, they were most frequently located in dendrites (Plate 2A).

Irreversible degeneration of the neurons started 3 or 4 d after the injection of cisplatin. In some zones, most neurons showed disappearance of all cytoplasmic organelles including the dense bodies (Plate 2B); in other zones, the neurons had, in addition, pyknotic nuclei (Plate 2C). Most neurons in a given zone appeared to degenerate simultaneously, and only infrequently did we find normal and degenerated neurons side by side. At 5 or 6 d after the administration of cisplatin, the degenerated zones were reduced to a soft tissue in which the histological study revealed only the presence of few degenerated nerve cells and numerous foci of macrophagic cells.

A careful comparison was made between the histological slides and electron micrographs from the brains of our cisplatin-treated embryos with those obtained previously from the embryos treated at the same age with lead nitrate.[16] It was observed that although the end result was similar in both cases (widespread degeneration of large zones of nervous tissue), the sequence of events leading to this final result was clearly different. In the case of brain necrosis by lead, multiple hemorrhagic foci proved to be the main initial step. The hemorrhagic foci were very rapidly surrounded by numerous macrophagic cells; no neuronal degeneration was observed before the third day after treatment, and the typical lysosomal dense bodies presently found in neurons after cisplatin treatment were very seldom seen in the case of brain tissues from lead-treated embryos. The complete liquefaction of vast zones of nervous tissue which we presently observed after cisplatin treatment was never observed after lead treatment.

V. GENERAL CONSIDERATIONS

A. MECHANISMS INVOLVED IN MICROPHTHALMIA

Microphthalmia (smaller than normal eye) is a malformation which appears spontaneously both in humans and in domestic animals.[17] It can also be produced experimentally through a great variety of teratogens.[18] The types of microphthalmia produced in the mechanisms explaining the resulting lesions vary not only with the teratogen used, but also, very importantly, with the developmental stage at which it is administered:

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* Plates 1 and 2 appear following page 46.

1. *Stage of evagination of the optic vesicles.* Very severe cases of microphthalmia appear to be produced, the same as anophthalmia, by alterations occurring very early in the development of the eye primordium.[19] Thus, the development of the eye can first be affected at the time in which the eye primordium evaginates from the prosencephalon. The evagination process requires changes in the shape of the cells of the wall of the prosencephalon; these changes in cell shape are, at least in part, instrumented by the cytoskeleton of the cell and specifically by microtubules. On this basis, anophthalmia or microphthalmia can be induced by the early administration of vincristine.[20] It is assumed that in this latter case the inhibition of microtubular function by vincristine would interfere with the evagination of the optic vesicle.
2. *Stage of formation of the optic cup.* After the optic vesicle is formed, it will invaginate and thus transform into an optic cup. This invagination can also be affected by agents inhibiting microtubular formation.
3. *Stage of growth of the optic cup.* Once formed, the optic cup starts a period of very rapid growth. The outer layer of the optic cup becomes a slow-growing pigmented monolayer, but the inner layer of the cup proliferates very rapidly, becoming stratified. During this stage of eye development, it is this highly proliferating inner layer which is most susceptible to the action of any type of antiproliferative agent. Cell proliferation at this stage is not only responsible for global increase in size of the eye, but also is responsible for the closure of the previously formed optic fissure. Antiproliferative agents acting at this third stage of development not only produce a decrease in size of the eye (microphthalmia), but also prevent the closure of the optic fissure and thus create a permanent opening which is known as coloboma. Microphthalmia is frequently associated with coloboma both in spontaneous and in experimentally induced microphthalmia; the reasons for this association are discussed below.
4. *Stage of eye expansion.* In a fourth stage of eye development, the cavity of the optic cup, limited in the outside by the developing lens, becomes filled with the primitive vitreum. It is believed that the vitreum is secreted under pressure and that the internal pressure created by this secretion stimulates the rapid expansion of the eye which takes place during this period. This developmental mechanism has been investigated in detail by Coulombre.[21] In painstaking microsurgical experiments, he introduced thin tubules into the cavity of the eyes from 5-d-old chick embryos. He thus found that vitreum leaked through the tubule and that, as a result of the decrease in internal pressure, the eyes failed to expand at a normal rate and microphthalmia resulted. If a solid rod rather than a tubule was inserted, fluids did not leak and normal eyes resulted. In these experiments, despite the fact that the eye failed to expand, the neural layer of the retina continued to grow at a rapid pace such that accommodation to the space available resulted in repeated folding of the neural layer as illustrated in Figure 2.

Coulombre[21] postulated that in the case of spontaneous microphthalmia, the presence of a coloboma would act exactly the same as the tubules inserted in his experiments. Inner fluids would escape, and a small eye with folded neuroretina would be the result. This concept explains very satisfactorily the fact that a large proportion of spontaneous cases of microphthalmia observed in man[22] and in genetically susceptible mouse strains[23] present both coloboma and retinal folding. The same can be said for the microphthalmia induced by antineoplasic agents such as cyclophosphamide.[24] In these experiments the antineoplasic agent probably acts during the third stage of eye development, i.e., before the optic fissure is closed. By preventing its closure, it would create a permanent coloboma and the decrease in the eye pressure due to escape of vitreum through the coloboma would, in turn, stop or reduce the growth of the eye. The fact that the expansion of the eye depends in part on the internal pressure and not solely on the mitotic rate of the optic cup explains the apparent contradiction of antiproliferative agents being able to inhibit the growth of the whole eye without affecting significantly the mitotic rate of the retina.

The above interpretation does not explain those cases in which microphthalmia is not accompanied by coloboma. This generally occurs when the teratogenic agent is administered slightly after the optic fissure has completed its closure. Thus, in Clavert's[24] experiments in the rabbit, coloboma appeared when cyclophosphamide was injected from the 8th to the 11th day of pregnancy, but very rarely when it was injected afte the 12th day.

In our experiments with cisplatin in the chick embryo, microphthalmia was in all probability due to decreased internal pressure and not to reduced growth rate of the optic cup as indicated by the folding of the retina. Since in these experiments microphthalmia was never accompanied by coloboma, the decrease in internal pressure was not due to escape of the vitreum. This reduction in internal pressure was more probably connected with the fact that, in all cases, the ciliary epithelium had degenerated. This ciliary epithelium is responsible for the secretion of the water and ions which contribute to the formation of the vitreum and the creation of the internal eye pressure.[24,25] In summary, we suggest that the microphthalmia resulted from a decrease in internal pressure due to deficient secretion by the ciliary epithelium rather than to escape of the vitreum. A similar mechanism might explain most spontaneous and/or experimental cases of microphthalmia in which there is retinal folding, but not coloboma. That this is the case is also suggested by the fact that this type of microphthalmia can be observed in fetuses from Zn-deficient pregnant rats.[26] Carbonic anhydrase, an enzyme required for the secretion of water and ions, is a Zn-containing enzyme and Zn deficiency probably might act by decreasing the formation of carbonic anhydrase in the ciliary epithelium. We are exploring further this experimental model by trying to produce identical results by testing substances which might inhibit the secretion of the ciliary epithelium without killing its cells.

B. MECHANISMS INVOLVED IN PRENATAL BRAIN LESIONS

Malformations of the nervous system are among the most frequent effects found in teratological experiments. This is probably due to the fact that growth and development of this system is a continuous process occurring during the whole embryonic, fetal, and early postnatal periods. The morphological characteristics and mechanisms of development of the nervous system have been discussed in great detail in numerous reviews and books.[27,28] Only the aspects of this process which are relevant to prenatal brain lesions will be covered. The first steps in the formation of the central nervous system occur very early in development. The neural plate becomes a neural groove and then both lateral lips of the groove contact each other dorsally so that the groove becomes transformed into a tube, the neural tube. This process of closure of the groove can be affected by genetic or environmental factors. Partial or total failure as well as delay in its completion might give rise to any one of a group of malformations known under the generic name of disraphiae (spina bifida, anencephalus, encephalocele, etc.).

Once the neural tube is closed, it starts a process of uninterrupted growth. Growth, however, does not occur at the same pace at all ages, and different regions of the tube grow at different rates at each stage of development. The rapidly growing neural tube accommodates to the space available by folding upon itself, forming three curvatures. The choroid plexuses differentiate early and secrete cerebrospinal fluid (CSF). The same as in the adult, CSF formed in the lumen of the tube circulates and moves into the subarachnoid spaces through orifices in the roof of the IV ventricle (rhombencepalon). Disturbances in the rates of growth of the cephalic part of the neural tube might affect the process of folding, alter the angle of the rhombencephalic curvature, and thus interfere with the circulation of CSF from the lumen to the subarachnoid space. These disturbances might produce a type of malformation known as obstructive hydrocephalus.

Upon reaching the fetal period, the caudal part of the neural tube, the same as most organs and structures in the embryo, has acquired its definitive shape and organization, although it continues to grow at a slow pace and to complete its functional differentiation. For this reason, this part of the nervous system, the same as occurs with most organs and structures in the embryo, very seldom is affected by teratogenic factors administered during this late period. Different is the case of the cephalic portion of the neural tube. The completion of such a complex organ as the brain requires a much longer period. The telencephalon will give rise to the cerebral hemispheres. In the case of bird embryos, the largest part of the hemispheres is constituted by the striatum which grows very actively between the 8th and 12th day.[4] It is at this stage in development that the telencephalon is most susceptible to the action of teratogens. This is illustrated in the experiments with cisplatin. Brain necrosis was produced with high frequency when administered on the 10th and 11th days of incubation.

In the case of mammals, morphogenesis of the telencephalon still continues further. Once the striatum has completed its growth, the overlying zone, known as the pallium, starts a period of rapid growth and forms the cerebral cortex. As a morphological expression of this rapid growth, the cortex folds, forming its typical gyri and sulci. Thus, in the case of mammals, the cerebral cortex still undergoes morphogenetic changes up to close to the end of the fetal period and is susceptible until this late stage to the action of teratogenic agents. An alteration in the growth rate of the neopallium if severe may induce different types of severe malformations such as microcephaly, lissencephaly, etc. If mild, the effects might be detectable only as behavioral problems during the postnatal period.

Several basic mechanisms govern the development of the nervous system.[27,28] Cell proliferation is, of course, the main mechanism of growth. Mitotic figures can be seen most frequently located in the inner layer of the neural tube (germinal or ependymal layer). At certain sites (cerebral and cerebellar cortices), proliferating cells migrate to the periphery. At all places and times, a certain proportion of the cells resulting from the proliferative process undergoes differentiation into the neuronal or the neuroglial cell lines. In this way, despite the fact that fully differentiated and functional neurons are already present at the early embryonic stages, immature cells in different stages of the differentiation process can be found not only during the embryonic period, but also during most or all of the fetal period. While programmed cell death is a basic mechanism in normal development of the nervous system,[28] nonprogrammed, excessive cell death is a frequent teratogenic mechanism. The effects are similar to those produced by inhibition of the mitotic rate as both result in a decreased growth rate. Thus, factors capable of inhibiting mitosis and/or killing immature cells are generally capable of inducing malformations of the disraphiae and obstructive hydrocephalus when acting during the embryonic period, yet are also capable of affecting the development of the brain when acting during the fetal period. Antineoplastic drugs are a good example of teratogens capable of this action.

Abnormalities of the nervous system induced by an antineoplasic agent were reported as early as 1948 by Haskin,[29] who administered nitrogen mustard to pregnant rats. Since then a large number of authors have reported similar abnormalities with different alkylating drugs, antimetabolites, and antimitotic alkaloids.[17,30] While antineoplastic drugs were found to act through different mechanisms, a common denominator in most of them was the presence at some stage in the development of the malformation of excessive (nonprogrammed) cell necrosis.

Depending on the dose or the nature of the drug used, cell necrosis was sometimes limited to the proliferating cells at the ependymal layer or to the neighboring layers containing cells in initial stages of maturation. In other cases, massive necrosis involving all cells in large regions of the neural tube were observed.[31]

Schweichel and Merker[32] studied the ultrastructural characteristics of degenerating cells in different tissues from rat and mouse embryos treated with different teratogens including several alkylating drugs and found that three types of degenerative processes might occur:

1. Type I degeneration was characterized by early nuclear pyknosis, followed by cytoplasmic condensation and fragmentation, followed by phagocytosis of cellular rests by neighboring cells.
2. Type II degeneration was characterized by early accumulation of lysosomal bodies followed secondarily by nuclear changes, fragmentation, and phagocytosis by neighboring cells.
3. Type III degeneration differed from the previous two by the absence of lysosomal participation and by the absence of reaction of neighboring cells.

Studying the effects of hydroxyurea on the embryonic nervous system of the mouse embryo, Herken et al.[33] found predominance of Type I necrosis and similar conclusions were reached by Köpf-Maier and Merker[14] using cisplatin. It was suggested that rapid pyknotic changes were the result of the action of alkylating agents on nuclear DNA.

Contrary to the above described observations, in our studies of brain necrosis induced by cisplatin, Type II necrosis was the predominant form. Thus, in our experiments, neurons showed a large number of lysosomal bodies 24 h after the administration of cisplatin, but pyknotic changes were not detected until 2 or 3 d after.

The differences between our observations in the chick embryo and those of Köpf-Maier and Merker[14] in the mouse are probably related to differences in the dose or rate of absorption by the embryos. In this regard, Schweichel and Merker[32] had indicated that cells with Type II necrosis were especially frequent in mass degeneration of tissues rather than in isolated degenerating cells.

On the other hand, it is of interest to compare the characteristics of brain necrosis induced by cisplatin with those found in brain necrosis induced by heavy metals. We have indicated above (see Section I, Introduction) that it has been suggested that cisplatin might owe its toxicity not only to its alkylating properties, but also to the presence of a metal in its molecule.[34]

Narbaitz et al.[16] conducted a histological and ultrastructural study on the brains from chick embryos injected with lead nitrate on the 11th day of incubation. A comparison has been presently made between those histological and ultrastructural observations and the present findings with cisplatin administered at the same age. It was found that the sequence of events leading to brain necrosis was different in each case. Thus, in the case of lead, brain necrosis appeared to be secondary to widespread hemorrhagic foci, while with cisplatin neuronal lesions appeared to occur either independently of, preceding, or even in the absence of hemorrhagic lesions. In this aspect, cisplatin behaves like most alkylating agents and not in the way which lead or other heavy metals do.

VI. SUMMARY

The characteristics of the response of embryos and fetuses to the action of toxic substances in general have been described. Apart from the initial stages of development, during which surviving embryos do not show permanent damage after toxic exposure, prenatal life can be divided into (1) an embryonic period during which malformations of numerous organs can be produced by a great number of teratogenic agents and (2) a fetal period in which most organs and tissues do not respond to toxic agents by developing malformations but rather with changes similar to those induced in the postnatal period by the same toxic agents. The brain is one of the exceptions to this rule since it can respond with malformations even when challenged during the later part of development.

Cell proliferation, together with cell migration, programmed cell death, and cell differentiation are the main mechanisms of morphogenesis. Antiproliferative drugs are, for this reason, important tools in investigating mechanisms of normal and abnormal development. Experiments with cisplatin illustrate well how one can take advantage of the properties of antineoplastic agents in order to clarify these mechanisms.

The results of our experiments testing cisplatin on chick embryos illustrate the fact that the response to toxic drugs depends on the age of administration. When administered on the fifth day of incubation (embryonic period), cisplatin produces microphthalmia not accompanied by coloboma. The demonstration of degenerative lesions in the ciliary epithelium suggests that this is the probable mechanism for this type of malformation. On the other hand, the injection of cisplatin at a later stage produced toxic lesions in liver and germ cells (lesions similar to those seen in the adult), but in addition, it produced brain necrosis. The characteristics of cisplatin-induced brain necrosis were shown to differ from those previously observed in lead-induced necrosis. It is suggested that cisplatin-induced necrosis is related more to its alkylating properties than to the action of the metallic nucleus present in the molecule.

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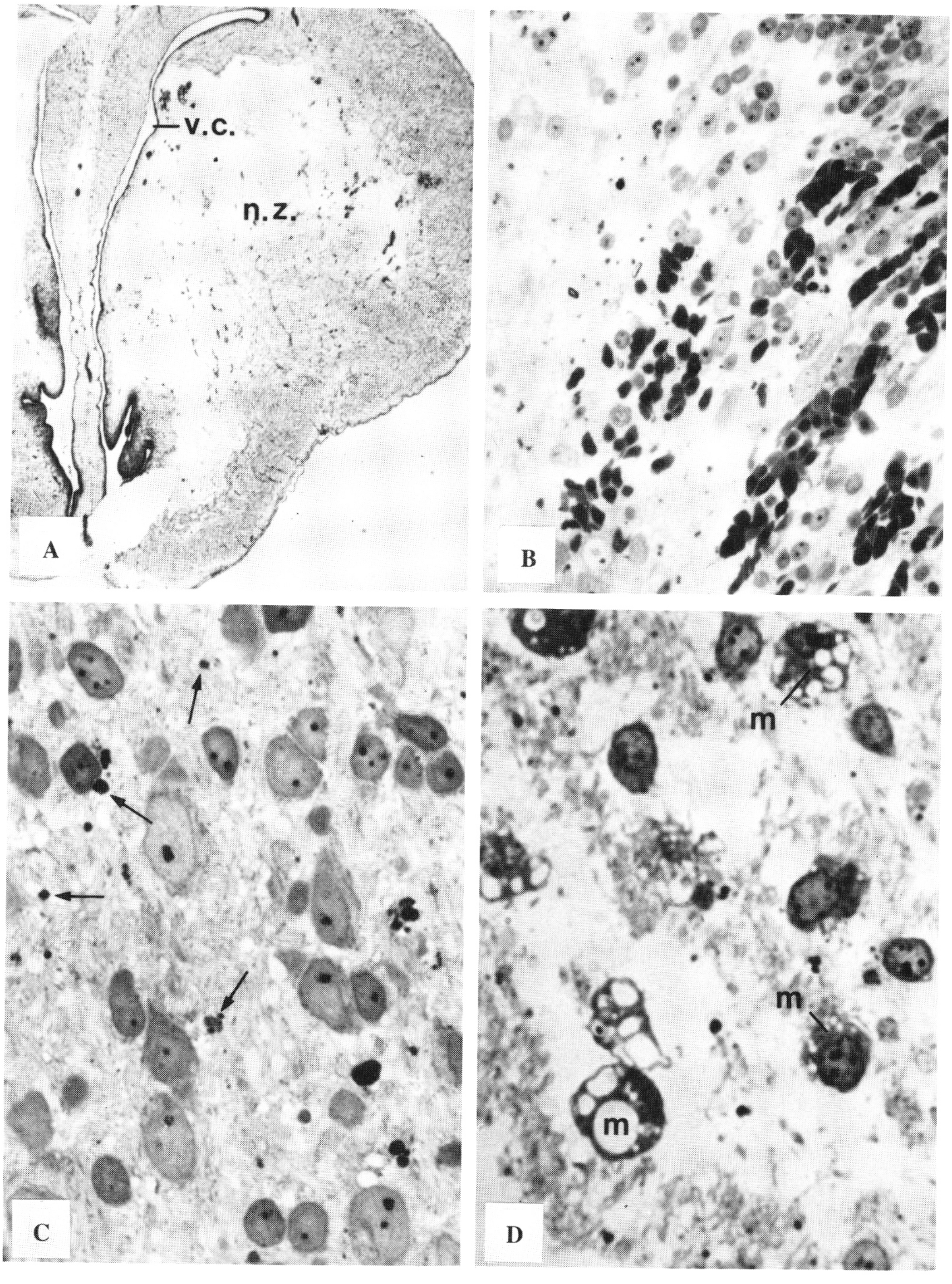

PLATE 1. (A) Light micrograph from a frontal section of the telencephalon from a 17-d-old chick embryo injected with cisplatin on the 11th day. Note zone of total necrosis in the inner core of the striatum. n.z.: necrotic zone; v.c.: ventricular cavity. (H.E.; magnification × 18.) (B) Cortical zone 24 h after the injection of cisplatin. Hemorrhagic foci are seen. Neurons appear unaffected. (Toluidine blue; magnification × 425.) (C) Cortical zone same embryo. Dark cytoplasmic bodies (arrows) have started to accumulate. Neuronal nuclei appear unaffected. (Toluidine blue; magnification × 1070.) (D) Cortical zone 3 d after injection. Accumulation of macrophagic cells (m). (Toluidine blue; magnification × 1070.)

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Chapter 4

PHARMACOLOGY OF CATECHOLAMINES

Arno Zaritsky

TABLE OF CONTENTS

I. Introduction 50
  A. Pharmacokinetics 50
  B. Pharmacodynamics 51

II. Adrenergic Receptors 52
  A. Receptor Regulation 52
  B. Ontogeny of Adrenergic Receptors 53

III. Ontogeny of Cardiovascular Function 54

IV. Endogenous Catecholamine Response 54
  A. Norepinephrine 55
  B. Epinephrine 55

V. Pharmacology of Specific Catecholamines 56
  A. Epinephrine 56
    1. Pharmacology 57
      a. Pharmacokinetics 57
    2. Indications and Dose 57
    3. Administration and Toxicity 58
  B. Norepinephrine 58
    1. Pharmacology 58
      a. Pharmacokinetics 59
    2. Indications and Dose 59
    3. Administration and Toxicity 60
  C. Isoproterenol 60
    1. Pharmacology 60
      a. Pharmacokinetics 61
    2. Indications and Dose 61
    3. Administration and Toxicity 61
  D. Dopamine 62
    1. Pharmacology 62
      a. Pharmacokinetics 63
    2. Indications and Dose 63
    3. Administration and Toxicity 65
  E. Dobutamine 65
    1. Pharmacology 65
      a. Pharmacokinetics 66
    2. Indications and Dose 66
    3. Administration and Toxicity 67

VI. Summary 68

References 68

I. INTRODUCTION

Catecholamines are used in pediatric patients for the treatment of asthma and croup. Additionally, they are often used in the treatment of critically ill children with septic, anaphylactic, or cardiogenic shock and in patients suffering a cardiac arrest. In these settings, catecholamines are administered to support the patient's cardiovascular system. Catecholamines, particularly isoproterenol, may also be used to reduce pulmonary artery hypertension and to increase the heart rate in the presence of heart block.

Critically ill infants and children often require the use of one or more inotropic agents to maintain adequate tissue perfusion. Catecholamines and other sympathomimetics are the most important group of inotropic agents currently available to treat these patients. Since each catecholamine has unique pharmacology, the clinical indications and potential toxicities differ from agent to agent. Ontogentic changes in the sympathetic nervous system may also influence the choice of drug. This chapter discusses developmental aspects of adrenergic receptor physiology and endogenous catecholamine responses, reviews the pharmacology of catecholamines, and highlights the cardiovascular actions, clinical indications, and toxicities of these agents. Much of the current information on catecholamine pharmacology is based on adult clinical or animal studies. Wherever possible, information obtained from pediatric patients or animal models will be highlighted.

Catecholamines are characterized by the presence of a core "catechol" structure that consists of a benzene ring hydroxylated at the 3 and 4 carbon positions and an ethyl side chain (Figure 1). When a catechol has an amino terminus on the ethyl side chain (ethylamine), it is called a catecholamine. Substitutions attached to the terminal amino group produce a variety of synthetic catecholamines with variable adrenergic receptor activity (Figure 1).[1] In general, increases in the size of the *N*-alkyl substituent augment the β-adrenergic receptor agonist activity. Sympathomimetic amines (such as metaproterenol and phenylephrine) have the same basic structure as catecholamines, but lack the hydroxyl groups on the third and fourth carbons of the benzene ring. The absence of these hydroxyl groups delays metabolism and greatly prolongs the actions of these amines compared to catecholamines. All catecholamines may be considered sympathomimetics, but all sympathomimetics are not necessarily catecholamines.

Since pediatric patients are developing and growing, drug action is modulated by developmental changes in pharmacokinetics and pharmacodynamics. These pharmacologic changes, which are partly related to changes in body water, maturation of enzyme systems, and changes in end-organ responsiveness, are outlined below.

A. PHARMACOKINETICS

The clinical use of inotropes requires an understanding of several important pharmacologic principles. It is beyond the scope of this chapter to discuss these pharmacologic principles in detail, but basic principles of catecholamine pharmacokinetics are reviewed briefly here. Whenever a drug is administered to a patient, its clinical actions are due to a complex interaction between the concentration of drug in the plasma, elimination from the body, diffusion to its site of action, and the response of the target tissue to the drug. Plasma drug concentration is modified by changes in the drug dose and pharmacokinetics, whereas the tissue response is influenced by changes in receptor and tissue responsiveness.

Pharmacokinetics is the mathematical expression of the time course of all processes leading to drug distribution and elimination. This time course is typically determined by quantifying drug concentration in the plasma compartment, although this approach may not be ideal since inotropic drug action occurs in the tissue and the plasma concentration may not necessarily represent the tissue concentration. In the critical care setting, most inotropic agents are administered by continuous intravenous infusion, making the kinetics relatively

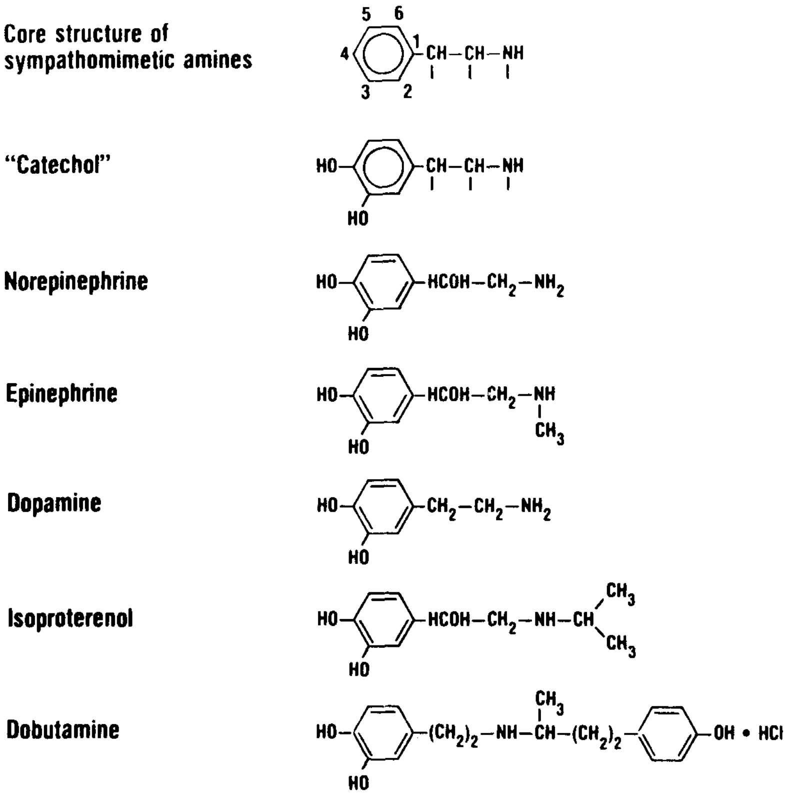
Core structure of sympathomimetic amines
5 6 4 1 3 2 CH–CH–NH
"Catechol"
HO HO CH–CH–NH
Norepinephrine
HO HO HCOH–CH2–NH2
Epinephrine
HO HO HCOH–CH2–NH CH3
Dopamine
HO HO CH2–CH2–NH2
Isoproterenol
HO HO HCOH–CH2–NH–CH CH3 CH3
Dobutamine
HO HO (CH2)2–NH–CH–(CH2)2 CH3 OH • HCl

FIGURE 1. Chemical structure of the catecholamines. (From Chernow, B., Rainey, T. G., and Lake, C. R., *Crit. Care Med.*, 10, 409, 1982. With permission.)

simple. Continuous infusion eliminates the need to consider drug absorption and subsequent distribution and the peak and trough drug concentrations seen with intermittent drug administration. With continuous drug infusion, steady-state plasma concentration is achieved in about five half-lives. Since the half-life of all catecholamines is in the order of 2 to 2.5 min, a new steady-state concentration, and thus maximal drug effect, is seen approximately 10 to 12 min after starting or changing the infusion rate. The pharmacokinetics of individual catecholamines are discussed under each agent.

B. PHARMACODYNAMICS

Pharmacodynamics is the relationship between drug concentration (again, usually measured in plasma samples) and drug effect. In the case of inotropic agents, measurable drug-induced physiologic action may be a change in cardiac output, blood pressure, and heart rate. When used clinically, the pharmacodynamic effects of inotropes are not related to the drug concentration in a simple manner since the patient's illness may influence the net hemodynamic effect observed.

In patients with circulatory shock, for example, decreased sensitivity to catecholamine infusions may be seen. This effect may be due to failure of drug within the plasma compartment to reach the active tissue site because of poor perfusion and/or diminished tissue receptor responsiveness mediated by the disease process producing the critical illness. As the patient's clinical condition changes the pharmacokinetics and pharmacodynamics of administered inotropes may also change, necessitating the frequent reassessment of the patient's cardiovascular state and adjustment of the infusion rate. In the discussion of individual inotropes that follows, statements regarding hemodynamic effects observed with

TABLE 1
Diseases and Conditions Altering Receptor Density on Effector Cells

Disease or condition	Receptor altered	Change
Congestive heart failure	β (heart)	Increased[a]
Sepsis	α (liver, vasculature)	Decreased
Myocardial ischemia	β (heart)	Decreased
Myocardial ischemia	α (heart)	Increased
Asthma[b]	β (lung, leukocytes)	Decreased
Cystic fibrosis	β (leukocytes)	Decreased
Fetal and neonatal life	α,β (heart, platelets, leukocytes)	Decreased
Agonist administration	α,β (heart, platelets, leukocytes)	Decreased
Antagonist administration	α,β (heart, platelets, leukocytes)	Increased
Hyperthyroidism	β (heart)	Increased
Hypothyroidism	β (heart)	Decreased
Glucocorticoids	β (heart, leukocytes)	Increased

[a] β-Adrenergic receptors are decreased in severe heart failure.
[b] If on β-agonist therapy for asthma.

From Zaritsky, A. and Eisenberg, M. G., in *Critical Care — State of the Art*, Vol. 7, Chernow, B. and Shoemaker, W. C., Eds., Society of Critical Care Medicine, Fullerton, CA, 1986, 485. With permission.

specific infusion doses should be recognized as being approximations at best and it should be recognized that individual adjustment is needed for each patient.

The impact of age and development on the pharmacodynamics of catecholamines has been studied by a number of investigators. There are structural and physiologic cardiovascular differences between the fetus, infant, child, and adult which have been summarized[2-5] and will not be repeated here in detail. These differences can alter the response of the immature patient to catecholamines and will be discussed in further detail under the pharmacology of each agent.

II. ADRENERGIC RECEPTORS

Adrenergic receptors are glycoproteins on the cell surface which function to transduce the signal from circulating or neuronally released catecholamines into a cell-specific function.[6,7] The actions of catecholamines are determined by their binding at three major classes of receptors: α-adrenergic, β-adrenergic, and dopaminergic (DA) receptors. There are two subtypes of each of these receptors, termed α_1 and α_2, β_1 and β_2, and DA_1 and DA_2.[6,8] Three of the four types of α- and β-adrenergic receptors mediate their cellular effects through stimulation (β-receptors) or inhibition (α_2-receptors) of adenylate cyclase activity. The α_1-adrenegeric receptor transduces the signal from receptor-agonist binding to cellular effect by increasing transcellular calcium flux through a recently described mechanism that results from phosphoinositol turnover at the cell membrane.[9,10] DA_1 receptors stimulate and DA_2 receptors inhibit adenylate cyclase activity.[11]

A. RECEPTOR REGULATION

Adrenergic receptor density on the cell surface is dynamic; the density of receptors can be modulated by a number of disease states or conditions (Table 1). Changes in receptor density can have important implications in the pharmacotherapy of the patient. Down-regulation (a decrease in the number of receptors on the cell surface) of β-adrenergic receptors in the myocardium of patients with chronic congestive heart failure results in decreased catecholamine sensitivity.[12] In endotoxic shock, β-adrenergic receptors are down-regulated in the liver, which may partially mediate the glucose dyshomeostasis seen in sepsis;[13,14] α_1-adrenergic receptor density and responsiveness are diminished in the peripheral vasculature, accounting for a portion of sepsis-mediated adrenergic vascular unresponsiveness.[15]

Receptor desensitization refers to a diminished cellular response with a normal receptor density. This condition has been most thoroughly studied in the β-adrenergic receptor.[16] Agonist binding to the β-adrenergic receptor produces receptor interaction with a coupling protein (N_s) that is regulated by guanine nucleotides. Coupling is required for successful activation of adenylate cyclase. Modulation of receptor-N_s interaction may have important effects on determining tissue sensitivity to β-adrenergic stimulation. Impaired interaction of receptors with N_s is seen in several clinical conditions (e.g., prolonged exposure to agonists, hypothyroidism, and hypoadrenalism).[16] The molecular basis for this "uncoupling" reaction is currently unknown, but is probably related to modification of the guanine coupling protein.[17] Thyroid hormones and steroids increase β-adrenergic sensitivity and evidence suggests that this may be at least partially mediated through a general increase in receptor coupling.[18,19]

Altered binding of receptors to N_s results in two affinity states of the β-adrenergic receptor. These affinity changes are modulated by small changes in plasma catecholamine concentration.[20] Changes in receptor affinity produce variations in adrenergic responsiveness, although our understanding of the β-adrenergic receptor coupling mechanisms is currently limited. It is likely that changes in receptor affinity have important implications in the actions of exogenous catecholamines. For example, repeated or prolonged exposure of the β-adrenergic receptor to an agonist results in an attenuated response which is partially mediated by altering the coupling state of the receptor.[21]

B. ONTOGENY OF ADRENERGIC RECEPTORS

Adrenergic receptor density may be altered by ontogenetic influences,[22] although there is limited information on the ontogenetic changes in catecholamine receptors. Decreased β-adrenergic receptor density and isoproterenol-induced cAMP formation is seen in granulocytes from neonates as compared to adults.[23] β-Adrenergic receptor density on lymphocytes appears to increase in an age-dependent manner, although α-adrenergic receptors on platelets do not change from infancy through childhood.[24] Decreased α-adrenergic receptor density occurs on newborn platelets and probably explains the diminished response of newborn platelets to epinephrine.[24] When interpreting studies which measure adrenergic receptor density on circulating blood cells, it is important to recognize that measured changes in receptor density may[26] or may not[27] be mirrored by similar changes in myocardial or pulmonary adrenergic receptors.

The ontogeny of myocardial α-adrenergic receptor density has been examined in dogs[28] and mice.[29] In both species, myocardial α-adrenergic receptor density increases early after birth and then declines to adult levels. In most species examined, myocardial α-adrenergic receptors produce a positive inotropic effect with little or no change in heart rate.[30] The role of these α-adrenergic receptors in human shock and critical illness is unclear.

Although most studies have reported a decrease in myocardial, lung, liver, fat, and brain adrenergic receptor density in immature animals,[31] Rockson and co-workers[32] observed an increased density of myocardial β-adrenergic binding sites in immature animals and an appropriate rate of cAMP generation in response to adrenergic stimulation. Even though the receptor density was increased, the inotropic response to isoproterenol and norepinephrine was diminished, suggesting a functional abnormality in the receptor system.[32]

The implications of decreased α- and β-adrenergic receptor density in infants may be reflected by diminished action of catecholamines on vascular smooth muscle of infants compared to adults.[33] Decreased vascular sensitivity to a variety of catecholamines has been a fairly constant,[34,35] albeit not invariant observation in immature animals.[36] It should be noted that few receptor studies have been done in humans. The application of findings in immature animals to humans may be inaccurate, but the reproducibility of observing decreased adrenergic responsiveness in multiple studies of immature animals and across different species suggests that age-related changes in adrenergic receptors have important clinical effects.

Even when adrenergic receptor density is normal or increased, altered catecholamine-produced inotropic, chronotropic, or peripheral vascular effects may be noted because of postreceptor influences. This circumstance is observed, for example, in neonatal and young dogs[32] and following either chronic exposure to catecholamines or chronic blockade of α- or β-adrenergic receptors.[16] Developmental changes in agonist affinity state are not well studied, but may prove to have important effects on the sensitivity of infants and children to catecholamines.

III. ONTOGENY OF CARDIOVASCULAR FUNCTION

In addition to maturational changes in adrenergic receptors and the sympathetic nervous system, important maturational changes in cardiovascular function occur in pediatric patients. The following discussion focuses on the important cardiovascular changes impacting on the response of the patient to catecholamines; more complete discussions of pediatric cardiovascular physiology can be found elsewhere.[36]

Maturational changes in intrinsic cardiac function impact on inotropic response. Ventricular compliance is reduced in the newborn and increases with age; the reduced compliance results from the greater amount of noncontractile tissue relative to contractile mass.[3] Additionally, the degree of filling of one ventricular chamber has a greater inhibitory influence on the filling of the other chamber in the young infant compared to the adult.[3] This is a common problem in pediatric patients with pulmonary hypertension (e.g., infants with chronic lung disease) in whom right ventricular pressure and volume overload impairs left ventricular filling.

Both the reduced ventricular compliance and the inhibitory effects of one ventricle on the other limit ventricular functional reserve in pediatric patients, particularly young infants. Stroke volume is smaller in infants and young children compared with adults when normalized to body weight.[36] Decreased compliance and stroke volume mean that the immature heart has a limited "preload reserve".[4,36] The increase in stroke volume following volume loading in newborns is smaller than expected,[37] and fluid resuscitation may therefore elevate ventricular filling pressures and systemic pressure to a greater extent in the newborn and the young infant compared to the adult.

Baseline heart rate,[36] contractility,[38] and cardiac index[39,40] are elevated at birth and in the early postnatal period. An elevated cardiac index results in a diminished cardiac reserve to meet the increased metabolic demands of a critical illness. Elevated baseline cardiac function also limits the proportional increase in output or contractility following inotropic stimulation. Thus, in studies comparing the response to catecholamine infusions in immature with mature animals, the ability to proportionately increase cardiac output or heart rate above baseline is limited in the immature animal, giving the impression that the immature subject has a diminished response, i.e., if the infant or child's heart is already functioning near maximal capacity, it may be difficult to achieve a further increase with inotropic stimulation.

IV. ENDOGENOUS CATECHOLAMINE RESPONSE

The neurohumoral response to illness has important effects on the pharmacodynamics of inotropes. Besides altering adrenergic receptor affinity state and density on the cell surface (*vide supra*), endogenous catecholamines exert vasoactive effects: stimulating heart rate and cardiac contractility, modulating peripheral vascular tone, and partly mediating the metabolic changes characteristic of many illnesses.[1,5] Thus, when a catecholamine is infused into a critically ill patient, the net hemodynamic effect reflects the pharmacodynamic action of the drug and the modifying influence of the patient's endogenous catecholamine response.

Maturation of the neurohumoral system occurs after birth. A great deal of information is known about neurohumoral maturation in several animal species, but the application of this data to the human is difficult since there are substantial maturational differences between species. For example, the sympathetic nervous system is relatively immature in newborn dogs[41] and rabbits[42] and relatively mature in newborn lambs.[43] Thus, delayed cardiac sympathetic innervation in the newborn puppy produces an increased dependency on blood-borne catecholamines from the adrenal gland[44] and decreased responsiveness to dopamine;[45,46] the latter is discussed in greater detail in the section on dopamine. The timing of myocardial sympthetic innervation in humans is unknown and it is difficult to relate findings in animals to humans. Even in the more mature lamb, adrenal catecholamines (i.e., epinephrine) have important tonic effects on myocardial contractility.[47]

A. NOREPINEPHRINE

The majority of plasma norepinephrine is derived from synaptic nerve clefts. Norepinephrine is the neurotransmitter of the sympathetic nervous system; it is released from sympathetic nerves and acts locally. The concentration of norepinephrine in the plasma is used as a marker for sympathetic nerve activity.[48] Although the plasma concentration is influenced by the rate of norepinephrine release, the plasma level is also determined by:

1. The rate of norepinephrine reuptake by the sympathetic nerve
2. The rate of metabolic degradation at the effector site
3. The rate of metabolic clearance from the plasma

Esler et al.[49] showed that a normal plasma norepinephrine concentration may be associated with an increased rate of norepinephrine release balanced by an increased rate of metabolic clearance. Plasma norepinephrine (and epinephrine) concentration is also influenced by the site of sampling, with epinephrine being increased and norepinephrine being decreased in forearm arterial vs. venous blood. Therefore, caution should be used in the interpretation of plasma norepinephrine concentrations as a reflection of sympathetic nervous system activity. Finally, elevations in plasma norepinephrine concentration reflect neuronal activity and are *not* equivalent to norepinephrine infusions, since circulating norepinephrine concentrations must exceed 1800 pg/ml to produce a clinically measurable hemodynamic effect.[51] However, these endogenous plasma concentrations are unusual in most stress states.

The release of norepinephrine from sympathetic nerves is controlled by a complex balance between presynaptic receptors (for catecholamines, acetylcholine, angiotensin, and other mediators)[52] and modulation by such other factors as pH, adenosine concentration, and prostaglandins which can either increase or decrease release.[52,53] Many of these hormonal or metabolic systems are abnormal in the ill patient and may modulate the local release and action of catecholamines.

B. EPINEPHRINE

Circulating epinephrine is largely derived from the adrenal gland with a small contribution from other chromaffin tissue. Unlike norepinephrine, epinephrine functions as a circulating hormone. Small changes in plasma concentration can produce significant alterations in hemodynamic effects.[54] Normal plasma epinephrine concentrations are in the range of 24 to 74 pg/ml, while concentrations of 75 to 125 pg/ml produce increases in heart rate and systolic blood pressure.[54]

Despite the limitations in the interpretation of plasma catecholamine concentrations noted above, it is apparent that the sympathetic nervous system functions as an important homeostatic mechanism to maintain blood pressure and cardiac output in response to shock and other stresses and that this response can be approximately quantitated by measurement of plasma catecholamine concentrations.

Hypoglycemia,[55] hemorrhagic hypotension,[56] trauma,[57,58] and cardiopulmonary arrest,[59] to name a few, are all associated with substantial increases in circulating norepinephrine and/or epinephrine concentrations. The extent of plasma catecholamine elevation has been correlated with the severity of congestive heart failure[60] and with the severity of injury early after trauma.[58] Thus, assessment of plasma catecholamines may prove to be a useful means of quantifying the severity of illness in critically ill patients. The increase in plasma catecholamines in critical illness may function in concert with other counterregulatory hormones to mediate some of the hemodynamic and metabolic alterations characteristic of stress,[61] although the degree of correlation between plasma catecholamine concentrations and cardiac effects is unclear.[62] In summary, endogenous catecholamine responses to critical illness influence the net hemodynamic response (pharmacodynamics) of exogenously administered catecholamines.

V. PHARMACOLOGY OF SPECIFIC CATECHOLAMINES

A. EPINEPHRINE

1. Pharmacology

As noted previously, epinephrine is an important endogenous hormone that is produced and released from the adrenal gland in response to stress. The direct cardiac effects of epinephrine are mediated through β_1-adrenergic receptors. Epinephrine shortens systole more than diastole, in part by increasing conduction through the AV node and Purkinje system. It accelerates transmission through the SA node directly and accelerates ectopic foci. Although epinephrine therapy may increase coronary blood flow, it may also increase myocardial oxygen demand more than oxygen delivery such that a mismatch occurs.[63] In addition, it decreases the refractory period of ventricular muscle predisposing the myocardium to arrhythmias.

When infused, the hemodynamic actions of epinephrine are determined by the infusion rate. It is of interest to note that substantially higher infusion rates (on a weight basis) are used in infants and children compared to adults.[5,64] At low rates (0.005 to 0.02 μg/kg/min in adults), epinephrine principally stimulates β-adrenergic receptors, whereas infusions up to 0.3 μg/kg/min in infants and children often produce a predominant β-adrenergic effect with little evidence of increased systemic vascular resistance. In general, the β-adrenergic range of infusion in pediatric patients is 0.05 to 0.3 μg/kg/min and results in peripheral vasodilation and increased heart rate and contractility. The net hemodynamic effects of this infusion rate are to widen the pulse pressure, decrease systemic and pulmonary vascular resistance, and increase stroke volume, left ventricular stroke work, and cardiac output, provided that the patient's circulating blood volume is adequate. As the infusion rate is increased, more α-adrenergic mediated effects are seen, resulting in increased systemic vascular resistance, elevation of blood pressure, and variable effects on cardiac output (the latter action is dependent on the ability of the myocardium to maintain stroke volume as afterload is increased).

Epinephrine has important effects on the respiratory system. Activation of β_2-adrenergic receptors in bronchial smooth muscle results in bronchodilation, which combined with an inhibition of mast cell degranulation (mediated through β_2-adrenergic stimulation) has beneficial effects in asthma.[65] Epinephrine is particularly important in the asthmatic patient since sympathetic nervous system innervation of bronchial smooth muscle is scant;[66] therefore, β-adrenergic-mediated bronchodilation is largely determined by the amount of circulating epinephrine.[67]

Epinephrine is a potent renal artery vasoconstrictor which limits its usefulness in patients with shock. Infusions as low as 0.035 μg/kg/min induce a 10% fall in renal plasma flow in man.[68] A portion of the vasoconstrictive effect of epinephrine is also probably mediated by increased renin activity following direct stimulation of β-adrenergic receptors of the juxtaglomerular apparatus.[69] The net effect is to reduce renal blood flow and urine output. Despite these limitations, in patients with low cardiac output, epinephrine may increase urine output by increasing cardiac output and therefore renal blood flow.[70]

Infusion of epinephrine to achieve plasma concentrations seen with exercise or stress causes plasma glucose, lactate, β-hydroxybutyrate, and free fatty acid concentrations to rise[54,71] and serum potassium[72,73] and phosphorus[74] concentrations to fall. Hyperglycemia is mediated by increased hepatic gluconeogenesis,[71] skeletal muscle insulin resistance,[75] and inhibition of insulin release.[54] Epinephrine concentrations up to 1000 pg/ml do not alter plasma alanine, glucagon, growth hormone, or cortisol levels.[54] Epinephrine-induced hypokalemia occurs through a β_2-adrenergic mechanism. Mean plasma potassium falls 0.8 meq/l in response to epinephrine concentrations achieved during myocardial infarction.[72,73] Coincident with the decline in potassium, T-wave flattening and QT_c prolongation were observed.[73] These electrophysiologic effects in combination with epinephrine-induced hypokalemia may predispose the critically ill patient to serious dysrhythmias. Similar decreases in plasma potassium are seen with the use of other β_2-agonists, such as agents used in asthma or to inhibit labor.[76]

a. Pharmacokinetics

Epinephrine pharmacokinetics have been examined in a number of studies in adults, but have not been studied in pediatric patients.[50,54] The previously described differences in dosage recommendations between adults and children suggest that (1) epinephrine clearance may be more rapid in children and/or (2) the infant and child's sensitivity (pharmacodynamic responsiveness) to epinephrine may be less than that observed in adults. Epinephrine is rapidly cleared from the plasma at mean rates of 35 to 89 ml/kg/min, depending on the site of sampling and the rate of epinephrine infusion.[50,54] These clearance rates are similar to those observed with dopamine[77,78] and dobutamine.[79,80] Clearance is largely by the liver and kidney which contain substantial concentrations of the enzymes catechol-*o*-methyl transferase and monoamine oxidase.[81] Splanchnic clearance is three times greater than renal clearance following infusion of epinephrine.[82] This efficient clearance results in a short half-life (about 2 min) requiring a continuous infusion to maintain hemodynamic effects. Perhaps more important is the degree of interindividual variation in epinephrine clearance reported in normal adults.[50,54] In critical illness, greater variation in clearance would be expected, emphasizing the importance of individual titration of the infusion rate.

2. Indications and Dose

Epinephrine infusions are most frequently used in pediatric patients at infusion rates of 0.05 to 0.3 μg/kg/min in the treatment of cardiogenic or septic shock.[5] Epinephrine may be particularly useful when combined with afterload reduction in cardiogenic shock[83] and is preferable to dopamine in pediatric patients in whom catecholamine stores may be depleted (see dopamine section, Table 2).

In the treatment of acute asthma, epinephrine may be administered subcutaneously in a dose of 0.01 mg/kg, up to 0.3 mg every 15 to 20 min. It is also administered subcutaneously in the treatment of acute allergic, local reactions (e.g., to bee stings) and may be administered intravenously (0.1 ml/kg of the 1:10,000 solution) in the treatment of anaphylaxis. In cardiac arrest, epinephrine is the most effective pharmacologic agent to restore spontaneous contractile function and may be administered intravenously (0.01 mg/kg) or endotracheally.[84]

TABLE 2
Suggested Uses of Catecholamines by Age[a]

Condition	Infant	Child	Adult
Cardiogenic shock	EPI or dobut DA[b]	Dobut DA or EPI	Dobut or DA EPI NE
Septic shock	EPI or dobut DA	Dobut EPI or DA	Dobut or DA NE or EPI
Hypovolemic shock	Not indicated	Not indicated	Not indicated
Shock from bradycardia	EPI or ISO	EPI or ISO	ISO or EPI
Anaphylactic shock	EPI	EPI	EPI
Decreased renal blood flow or urine output	DA	DA	DA

Note: DA, dopamine; EPI, epinephrine; dobut, dobutamine; NE, norepinephrine; ISO, isoproterenol.

[a] Listed in order of preference.

[b] DA at low infusion rates (1 to 2 μg/kg/min) may be used in combination with other catecholamines in shock to help maintain renal blood flow. DA is relatively contraindicated in patients with pulmonary artery hypertension.

From Zaritsky, A. and Eisenberg, M. G., *Critical Care — State of the Art*, Vol. 7, Chernow, B. and Shoemaker, W. C., Eds., Society of Critical Care Medicine, Fullerton, CA, 1986, 485. With permission.

3. Administration and Toxicity

Epinephrine (adrenalin) is available in several forms: prediluted in syringes (1:10,000 solution; 0.1 mg/ml) for use in cardiac arrest and anaphylaxis and in vials for subcutaneous administration (1-ml vials; 1:1,000 solution; 1 mg/ml) and the preparation of intravenous infusions (30-ml vials; 1 mg/ml).

Epinephrine should preferably be administered through a central venous line or at least through a secure peripheral catheter, since infiltration of a peripheral venous administration site can result in local ulceration. If infiltration occurs and is recognized early, local injection of the site with 1 to 5 mg of phentolamine in 1 to 5 ml of saline (depending on patient size and the size of the infiltrate) may be effective. The epinephrine infusion rate should be controlled by a constant infusion pump to avoid inadvertent boluses. Epinephrine is compatible with a number of intravenous solutions (Table 3). Alkaline solutions should be avoided as diluents for epinephrine and other catecholamines since they are inactivated at the higher pH.

Endotracheal administration is reserved for patients in cardiac arrest or severe anaphylaxis in whom vascular access is not readily available. To improve absorption by this route, it is important to deliver the drug deeply into the airway, which may be accomplished by administration through a small feeding tube or other suitable catheter followed by flushing with saline and manual hyperventilation.[85,86] Epinephrine-induced toxicities include restlessness, fear, throbbing headache, tachycardia, tachydysrhythmias (PVCs, ventricular tachycardia, and ventricular fibrillation), severe hypertension with secondary cerebral hemorrhage, and myocardial ischemia resulting from an increase in myocardial oxygen demand relative to myocardial oxygen delivery.

B. Norepinephrine

1. Pharmacology

Norepinephrine is the neurotransmitter of the sympathetic nervous system and is the biosynthetic precursor of epinephrine, differing only by a methyl group on its amino terminus

TABLE 3
Preparation of Catecholamine Infusions

Drug	How supplied[a]	Preparation[b]	Dose
Epinephrine	1-mg (1-ml) ampule or 30-ml vial (1 mg/ml)	0.6 × body weight (kg) is mg added to make 100 ml	Then, 1 ml/h delivers 0.1 μg/kg/min
Norepinephrine	4-mg ampule; 4 ml of fluid (1 mg/ml)		
Isoproterenol	1-mg ampule; 5 ml of fluid (0.2 mg/ml)		
Dopamine	200-mg ampule (5 ml; 40 mg/ml); or 400-mg (10 ml; 40 mg/ml) prefilled syringe	6 × body weight (kg) is mg added to make 100 ml	Then 1 ml/h delivers 1 μg/kg/min
Dobutamine	250-mg lyophilized vial, reconstitute with 10—20 ml of sterile H_2O or D_5W; also in prefilled syringe (400 mg/5 ml)		

[a] Protect ampules from light.
[b] Diluent may be D_5W, $D_{10}W$, NS, RL, D_5NS; avoid alkaline solutions.

(Figure 1). It possess both α- and β-adrenergic receptor activity. Low infusion doses produce mainly β-adrenergic effects, including increased cardiac contractility, conduction velocity, and chronotropy with little change in peripheral vascular resistance. More commonly, in the doses used during hypotensive shock, mixed α- and β-adrenergic effects occur. Peripheral vascular resistance is increased by α_1-adrenergic-mediated vasoconstriction. Cardiac contractility, cardiac work, and stroke volume all increase if the augmentation in afterload is tolerated by the ventricle. Chronotropy is generally blunted by baroreceptor-mediated vagal effects which slow the heart rate in response to norepinephrine-induced increase in blood pressure.

As with epinephrine, norepinephrine is a potent renal and splanchnic vasoconstrictor which limits its clinical usefulness.[87] It vasoconstricts the pulmonary as well as the systemic vascular bed and should be used with caution in patients with pulmonary artery hypertension. Norepinephrine infusion at 5.0 μg/min in normal adults elevates blood glucose, glycerol, β-hydroxybutyrate, and acetoacetate.[51] The metabolic effects of infusions in pediatric patients and during critical illness have not been reported. Studies in immature animals demonstrate potentially important, but complex, age-dependent changes in peripheral and central cardiovascular responses to norepinephrine,[34,88] making pharmacotherapeutic recommendations difficult.

a. Pharmacokinetics

As with epinephrine, the kinetics of norepinephrine in pediatric patients have not been reported. In adults, norepinephrine is rapidly cleared from the plasma following intravenous administration with an average half-life of 2 to 2.5 min, although substantial interindividual variation has been noted.[89] Norepinephrine is cleared by enzymatic degradation in the liver and kidney and by uptake and degradation in neuronal and nonneuronal effector organ sites.

2. Indications and Dose

Norepinephrine administration has limited usefulness in pediatric patients. The major indication is to elevate blood pressure in hypotensive patients who have failed to respond to adequate volume resuscitation and other, less potent inotropes. The most frequent clinical condition generating this state is septic shock, and norepinephrine can help maintain perfusion pressure and urine output in this setting.[90,91]

Norepinephrine may also be useful in cardiogenic shock complicated by hypotension, since the major determinant of myocardial oxygen delivery is the diastolic blood pressure-left ventricular end-diastolic pressure gradient.[92] The goal in cardiogenic shock is to increase mean arterial pressure to 50 to 70 torr, depending on the age of the patient. Use of a potent vasoconstrictor, however, must be balanced against the increase in ventricular afterload which heightens myocardial oxygen demand; therefore, norepinephrine should only be considered a temporizing measure in cardiogenic shock therapy.

An additional concern with norepinephrine is renal vasoconstriction compromising renal function. Low-dose dopamine diminishes the vasoconstrictive action of norepinephrine in dogs.[93] The clinical combination of dopamine and norepinephrine may therefore provide both the desired increase in coronary perfusion pressure and maintain adequate renal function.

Norepinephrine may also be added to gastric lavage solutions used in the treatment of acute GI bleeding, with a recommended mixture being 16 mg of norepinephrine added to 200 ml of iced saline.[94] In pediatric patients, initial norepinephrine infusion rates are 0.05 to 0.1 μg/kg/min and are subsequently titrated up to 1.0 μg/kg/min until the desired change in blood pressure is achieved.

3. Administration and Toxicity

Intravenous infusions of norepinephrine bitartrate are constituted as seen in Table 3. Norepinephrine infusions should preferably be given through a central vein. Careful monitoring of arterial pressure, peripheral perfusion, and renal function is necessary during norepinephrine infusions to prevent organ ischemia and excessive increases in ventricular afterload. Inadvertent boluses may precipitate profound hypertension with resulting myocardial infarction or cerebral hemorrhage.[95] Infiltrated infusions may produce local skin necrosis and ulceration and if recognized early should be treated with phentolamine injection (see Section V.A.3). Anxiety, respiratory difficulty, palpitations, chest pain, and transient headaches also occur.

C. ISOPROTERENOL

1. Pharmacology

Isoproterenol is a synthetic, *N*-alkylated catecholamine similar in structure to epinephrine (Figure 1). It is a potent β-adrenergic agonist and therefore has potent effects on the heart, stimulating an increase in cardiac contractility, heart rate, and conduction velocity. It also shortens AV nodal conduction and may incite either ventricular or atrial dysrhythmias. Stimulation of peripheral β_2-adrenergic receptors results in vascular smooth muscle relaxation; systemic vascular resistance, and diastolic blood pressure fall. Since β_2-adrenergic vascular receptors are most prevalent in the skeletal muscle vascular bed, cardiac output may be redirected from the splanchnic bed to the skeletal muscle bed, producing a ''splanchnic steal''.[96]

The net hemodynamic effect produced by isoproterenol infusion is an increase in cardiac output, provided circulating blood volume is adequate. When circulating blood volume is low, vasodilation may impair venous return and cardiac output may fall. Pulse pressure increases due to a rise in systolic pressure which is generated by enhanced cardiac contractility, while the fall in diastolic blood pressure is mediated by peripheral vasodilation. Much of the increase in cardiac output is often due to an increase in heart rate rather than stroke volume, particularly in pediatric patients.[96,97]

Isoproterenol also relaxes pulmonary vascular and bronchial airway smooth muscle, decreases pulmonary vascular resistance, and reverses bronchospasm. By overcoming hypoxic pulmonary vasoconstriction, isoproterenol can increase intrapulmonary shunt and may decrease arterial oxygen tension when used in patients with parenchymal lung disease.

Since heart rate and contractility are increased, myocardial oxygen demand is enhanced. At the same time, isoproterenol-induced decrease in diastolic filling time and diastolic coronary perfusion pressure may impair myocardial oxygen supply, resulting in myocardial ischemia.[98] Isoproterenol does not produce the same degree of hyperglycemia as epinephrine, probably because β-adrenergic stimulation enhances insulin release, whereas α_2-adrenergic stimulation (as produced by epinephrine) markedly inhibits insulin release.[99]

a. Pharmacokinetics

Following intravenous administration in adults, isoproterenol is rapidly cleared from the plasma with a half-life of about 2 min.[100] Plasma clearance in infants and children following continuous infusion has not been reported. It is noteworthy that recommended infusion rates are, on a weight basis, at least ten times higher in infants and children compared with adults;[5,64] this fact suggests that clearance may be higher in children and/or sensitivity may be diminished. Isoproterenol is largely cleared in the liver and to a lesser extent is taken up by effector organs throughout the body. It is also well absorbed from the tracheobronchial tree and is thus available in an aerosol form for treatment of asthma, although more selective β_2-adrenergic agonists, such as metaproterenol and albuterol, have largely replaced aerosolized isoproterenol.

2. Indications and Dose

Once a popular inotrope, isoproterenol has fallen out of favor because (1) a propensity to produce myocardial ischemia and excessive tachycardia ensues and (2) more selective inotropes are available. Isoproterenol may be used to treat hemodynamically significant bradycardia, particularly in the setting of heart block, but should only be considered a temporizing measure until more definitive therapy, such as cardiac pacing, is obtained.[101] Bradycardia in pediatric patients often results from hypoxemia or another airway problem or following severe myocardial ischemia, such as in the postarrest patient. In the former group, attention to airway management supersedes pharmacologic therapy, while in the latter group, low-dose epinephrine infusion may be useful and has the advantage of maintaining diastolic coronary perfusion pressure better than isoproterenol.

Isoproterenol has been effective in pediatric patients with status asthmaticus[102] and pulmonary artery hypertension.[103] Indeed, isoproterenol has been used to help assess the reversibility of pulmonary hypertension in pediatric patients prior to surgery in certain forms of congenital heart disease. It also is used to reduce pulmonary artery pressure in the postoperative period.[103,104] Finally, isoproterenol may be used as an inotrope, although other agents are available which have fewer side effects.

In pediatric patients initial infusion rates are 0.05 to 0.1 μg/kg/min and are adjusted to produce the desired hemodynamic effect. As with other catecholamines, infusions should be administered through a secure intravenous line using a calibrated infusion pump, and the patient's heart rate and blood pressure should be continuously monitored.

3. Administration and Toxicity

The parenteral form of isoproterenol is available in 5-ml vials containing 1 mg (1:5,000 solution). Infusions are prepared as seen in Table 3. In children (>10 kg), using the formula in Table 3 results in the need for many vials of isoproterenol. For example, a 20-kg child would need 12 vials. The simplest way to adjust the formula is to make a 1:10 dilution. Thus, in a 20-kg patient, adding 1.2 mg (rather than 12mg) to make 100 ml will result in a solution such that each 10 ml/h (rather than 1 ml/h) will deliver 0.1 μg/kg/min.

The major side effects of isoproterenol are tachycardia and tachydysrhythmias, particularly ventricular tachycardia. Myocardial ischemia may result from the unfavorable action of isoproterenol on myocardial oxygen demand relative to oxygen delivery[92,98] and has been reported in pediatric patients treated for status asthmaticus.[105] Palpitation, headache, and flushing of the skin are common, whereas nausea, tremor, dizziness, and weakness are less common side effects.

D. DOPAMINE

1. Pharmacology

Dopamine is the immediate precursor of norepinephrine in the endogenous catecholamine biosynthetic pathway and differs from norepinephrine by the absence of a β-hydroxyl group (Figure 1). Dopamine also serves as a neurotransmitter in both the central and peripheral nervous systems.[106] In the latter, it modulates autonomic activity at sympathetic ganglia, decreases gastrointestinal activity and aldosterone synthesis and release,[107] and increases renal blood flow.[107,108] When infused in pharmacologic concentrations, dopamine has complex actions due to mixed direct and indirect sympathomimetic effects.

Unlike the other catecholamines, the hemodynamic effects of dopamine are due both to dopamine-stimulated release of norepinephrine from sympathetic nerves and direct stimulation of α-, β-, and DA receptors.[46,109] When isolated, perfused ventricular muscle strips from canines of different ages are exposed to progressive increases in perfusate dopamine or isoproterenol concentrations; little inotropic response to dopamine was observed in puppies from 0 to 7 d. An increasing response was observed with aging. No difference in response to isoproterenol was observed throughout the age range studied.[46] Pretreatment with reserpine to deplete endogenous norepinephrine stores eliminated the age-related improvement in dopamine response. This study suggested that the blunted inotropic response to dopamine in younger animals results from delayed sympathetic nervous system innervation of the ventricular myocardium and thus diminished releasable stores of norepinephrine. It also suggested that as much as 50% of the hemodynamic action of dopamine may be produced by norepinephrine release.[46] In clinical studies, dopamine infusions increase plasma norepinephrine in a dose-dependent manner.[78,110] Further, the hemodynamic effect of dopamine is less pronounced than that observed with a direct-acting catecholamine, such as dobutamine, in clinical conditions characterized by myocardial norepinephrine depletion.[111,112]

When infused at 2 to 5 μg/kg/min in normal subjects, dopamine increases cardiac contractility and cardiac output with little change in heart rate, blood pressure, or systemic vascular resistance.[109,113] Doses up to 10 μg/kg/min in normal subjects further increase cardiac output with small elevation in heart rate and blood pressure.[113] Renal blood flow and urine output increase at doses of 0.5 to 2.0 μg/kg/min secondary to selective action at dopaminergic receptors.[114] Sodium excretion is enhanced with both the increase in renal blood flow and the inhibition of proximal tubular sodium reabsorption.[115] Although the salutary effect of dopamine on renal blood flow may be lost at higher doses due to predominant α-adrenergic effects,[109] further improvement in renal function may occur at higher dopamine infusion rates due to improved global cardiac output. Based on studies in adults with congestive heart failure, infusion rates in excess of 10 to 15 μg/kg/min produce increasing α-adrenergic effect with elevation in systemic vascular resistance and subsequently mean arterial pressure.[116] However, in adults with septic shock[117] and neonates with hypotensive shock,[118] higher dopamine infusion rates further improve urine output. Indeed, infusions in excess of 20 μg/kg/min consistently increased urine output in newborns concomitant with an improvement in blood pressure.[118]

Age-related effects of dopamine in the renal vascular bed have been described. Dopamine-mediated increases in renal blood flow are only seen in older puppies[45] and piglets.[119] Diminished dopamine action in immature canine kidneys, however, does not appear to be on the basis of decreased dopamine receptor density.[120] Clinical studies examining the renal effects of dopamine in immature patients are contradictory. Dopamine infusion (0.5 to 2 μg/kg/min) improves urine output, sodium excretion, and creatinine clearance in premature neonates,[121] but has no effect on glomerular filtration rate or urine output at infusion rates of 5 to 15 μg/kg/min in infants following open-heart surgery.[122] These disparate findings may be partly related to studying different disease states which can alter pharmacodynamic response.

In patients with pulmonary hypertension, dopamine infusions may lead to further increases in mean pulmonary artery pressure[123,124] and enhancement in hypoxic pulmonary vasoconstriction.[125] Recent data suggest that this may be partly related to enhanced α_2-adrenergic sensitivity in the pulmonary vasculature when baseline pulmonary vascular tone is elevated.[126] In the absence of pulmonary hypertension, dopamine increases pulmonary blood flow with little change in mean pulmonary artery pressure or pulmonary capillary wedge pressure.[109] At low-dose infusions (2 μg/kg/min) dopamine appears to decrease right ventricular afterload by relaxing prearteriolar tone.[127] Dopamine constricts capacitance veins which may raise pulmonary capillary wedge pressure.[128,129] Serious consequences may then result in increased myocardial wall tension and therefore myocardial oxygen demand, as well as in worsening hydrostatic pulmonary edema.[111]

Dopamine has a number of metabolic effects which may be important in the critically ill patient. Stimulation of dopamine receptors located in the zona glomerulosa of the adrenal cortex decreases aldosterone secretion.[130] Conversely, dopamine receptor blockade (e.g., following the administration of metoclopramide) increases plasma aldosterone concentration.[131] Dopamine inhibits thyrotropin-stimulating hormone (TSH) and prolactin release.[132] The former blunts the response to thyrotropin-releasing hormone (TRH), making discrimination between the patient with hypothyroidism vs. the euthyroid-sick syndrome more difficult if the patient is receiving dopamine. Insulin secretion is also inhibited by a direct action of dopamine on pancreatic islet cells,[133] although the clinical importance of this effect during dopamine infusion is unclear.

a. Pharmacokinetics

Following intravenous administration, dopamine is rapidly cleared from the plasma by a biphasic process with a terminal elimination half-life of 9 min.[78] A number of studies (detailed below) suggest that dopamine clearance may be faster in infants and children compared to adults, since infusion rates in pediatric patients are often higher than those required in adults, i.e., if clearance is higher, steady-state plasma concentrations with a given infusion rate in children will be lower than that obtained in adults. Despite this logic, steady state plasma clearance of dopamine (50 to 70 ml/kg/min) is similar in adults and children.[77,78,134]

2. Indications and Dose

Dopamine is frequently used to support the circulation following cardiac surgery. Lang and co-workers[129] treated five children with dopamine following cardiovascular surgery (mean age, 8 months) and found that heart rate, blood pressure, and cardiac output did not increase until infusion rates were greater than 15 μg/kg/min. Observed increases in cardiac output at higher infusion rates were related to an increase in heart rate rather than improved stroke volume. This is a much different response than that observed in adults where the inotropic action of dopamine was observed at lower infusion rates and increased during a 24-h observation period postbypass graft.[135] Lang et al.[129] support the contention that infants are less responsive to dopamine, but this study was not controlled and included a heterogenous group of patients. Perez and colleagues[118] in a prospective study of dopamine treatment for hypotension in five newborns found that an infusion rate greater than 20 μg/kg/min was required to achieve adequate blood pressure, capillary refill, and urine output.

An evaluation of dopamine therapy in 24 children (2 d to 18 years, mean age of 39 months), most of whom had congenital heart disease and shock from various medical and surgical causes, revealed different results.[136] The dopamine infusion was adjusted to the desired response (a >15% increase in systolic blood pressure) and more than half of the patients responded favorably at a mean dose of 8.3 μg/kg/min in the responders. In this group, blood pressure increased, whereas heart rate did not. More recent studies[137,138] reported that relatively small dopamine doses (2 to 5 μg/kg/min) improved blood pressure and myocardial performance in neonates. These conflicting results illustrate the limitations of clinical studies which often include patients with diseases of diverse etiologies.

In a more carefully controlled study, Padbury and co-workers[77] related changes in measured plasma dopamine concentration to cardiovascular responses in newborn infants. They found that neonates were quite sensitive to dopamine where infusion rates as low as 0.5 to 1.0 μg/kg/min produced important effects on blood pressure and cardiac output (measured by echocardiography). Heart rate increased at infusion rates of 2 to 3 μg/kg/min. They ruled out a pharmacokinetic basis for this observation, since they found that dopamine clearance was not related to age or birth weight and was similar to that previously reported in adults.[78]

Despite this beneficial effect, when compared to dobutamine, dopamine produces a relatively smaller enhancement of left ventricular contractility and it increases myocardial oxygen demand.[139] Differences in the hemodynamic response to dopamine and dobutamine in the postoperative period may be related to the state of the ventricle.[140] In normal ventricles, the chronotropic response of dobutamine is greater than dopamine. In volume-loaded ventricles (patients with enlarged ventricles, as might occur in a child with a ventricular septal defect), both drugs had similar effects on heart rate and cardiac output, but dobutamine caused a greater reduction in systemic and pulmonary vascular resistance.[140] Neither agent (at 5 μg/kg/min) produces a significant change in hemodynamics in the pressure-loaded ventricle (e.g., patients with valvular stenosis and increased ventricular muscularity). Based on these studies, dobutamine appears to be a superior inotrope when compared with dopamine following cardiac surgery.

Combined administration of dopamine and dobutamine may have advantages over the administration of either agent alone in cardiogenic shock.[141] In adults, dopamine alone (15 μg/kg/min) consistently:

1. Increased mean arterial pressure and pulmonary capillary wedge pressure
2. Had variable effects on stroke index
3. Reduced PaO_2

Dobutamine alone (15 μg/kg/min):

1. Failed to increase mean arterial pressure
2. Improved stroke volume
3. Did not affect PaO_2

probably because dobutamine has less effect on pulmonary capillary wedge pressure.[142] The combination of dopamine and dobutamine (7.5 μg/kg/min each) had the most beneficial effects: mean arterial pressure, cardiac index, and stroke volume index all increased with no change in pulmonary capillary wedge pressure, mean pulmonary artery pressure, or PaO_2.[141] All three infusions increased intrapulmonary shunt. This effect is common to inotropes which increase cardiac output and is due to improved perfusion of poorly ventilated lung segments.[143]

As in cardiogenic shock, dobutamine is superior to dopamine in chronic heart failure.[142]

Based on animal studies, the inotropic response of dopamine is attenuated in chronic heart failure because myocardial norepinephrine stores are depleted in this condition.[112] In addition, dopamine loses its inotropic effect after 24 h of infusion in experimental myocardial infarction, presumably because of depletion of myocardial norepinephrine stores. Further, dopamine accentuates myocardial norepinephrine release which may more rapidly deplete stores.[144]

In septic shock, dopamine improves cardiac output, although intrapulmonary shunting may increase as well.[145] The latter can be prevented by the application of positive end-expiratory pressure (PEEP).[145] Since many septic patients are hypotensive, dopamine has the advantage of increasing systemic vascular resistance and therefore blood pressure and may be preferable over dobutamine in this clinical setting.[117,146] An additional advantage of dopamine is its beneficial effect on urine output.[117] Despite these advantages, dopamine has the disadvantage of increasing pulmonary capillary wedge pressure and pulmonary artery pressure in some septic patients.[117,145]

The major clinical benefit of dopamine is that it causes a selective increase in renal and splanchnic blood flow. A low-dose infusion (1 to 4 μg/kg/min) augments urine output following cardiopulmonary bypass[147] and in patients with oliguria and critical illness.[148] Dopamine may also antagonize the vasoconstrictive action of norepinephrine and other adrenergic vasoconstrictors.[93] In experimental studies, it improves blood flow and protein synthesis in the postischemic liver.[149]

In pediatric patients, the pharmacodynamic effects of dopamine are further complicated by ontogenetic changes in response.[22] In experimental animal studies, the more immature the animal, the smaller the relative hemodynamic response compared to adults.[46,119] Clinical studies reveal more consistent salutary effects of dopamine in premature neonates as infusions of 0.5 to 2.0 μg/kg/min improve urine output, sodium excretion, and creatinine clearance.[121] Dose-dependent improvement in blood pressure and cardiac output in premature infants is seen at infusion rates between 2 to 8 μg/kg/min.[77] Recommendations for the use of dopamine and other catecholamines in pediatric patients are seen in Table 2.

In general, infusion rates of 0.5 to 2 μg/kg/min result in selective dopaminergic actions on the renal and splanchnic vasculature. At infusion rates between 5 to 10 μg/kg/min, β-adrenergic effects usually dominate. Infusions between 10 to 20 μg/kg/min have mixed α- and β-adrenergic effects, while infusions in excess of 20 μg/kg/min have predominant α-adrenergic effects. It is important to remember that these are approximate dosage guidelines. Alterations in endogenous catecholamine response or receptor density can change dopamine pharmacodynamics.

3. Administration and Toxicity

Dopamine is available in a number of commercial formulations, and infusion for pediatric patients may be prepared as seen in Table 3. As with other catecholamines, dopamine should not be mixed in an alkaline solution.

Nausea, emesis, and tachyarrhythmias are the most frequent side effects.[150] Anginal pain, myocardial ischemia,[144] serious hypertension, and profound vasoconstriction may occur.[144,150] In patients dependent on hypoxic ventilatory drive, dopamine may depress ventilation and worsen hypoxemia.[151]

E. DOBUTAMINE

1. Pharmacology

Dobutamine was developed following the systematic modification of the catecholamine molecule in the search for an agent that would have selective inotropic activity with little peripheral vascular effect.[152] Dobutamine has a large substitution on the amino terminus of the catecholamine molecule (Figure 1), and it is the only catecholamine administered as a racemic mixture. This racemic mixture provides dobutamine with its characteristic β_1-adrenergic selectivity: the (−) isomer is an α-adrenergic agonist and the (+) isomer acts as a competitive α-adrenergic receptor antagonist.[153] The (+) isomer is also the more potent form at the β-adrenergic receptor, although both isomers produce inotropic and chronotropic actions.[153]

The hemodynamic effect of dobutamine is dependent on drug dose. At usual infusion rates (5 to 15 μg/kg/min), the predominant effect of dobutamine is on the heart with an increase in contractility and a relatively smaller increase in heart rate. The comparatively selective inotropic action of dobutamine is probably multifactorial and due in part to the presence of both β_1- and β_2-adrenergic receptors in the sinoatrial node producing chronotropic effects. Dobutamine has a higher affinity for the β_1-adrenergic receptor.[154] Isoproterenol markedly stimulates both β-receptor types and thus produces a greater direct chronotropic response compared to dobutamine. Attenuated α-adrenergic vasoconstrictive effects in the peripheral vasculature are further balanced by a modest β_2-adrenergic effect so that peripheral vascular resistance is little changed.[155] Dobutamine generally lowers central venous and pulmonary wedge pressure and has little effect on pulmonary vascular resistance. Like other inotropes, dobutamine can increase intrapulmonary shunt by augmenting cardiac output and thus perfusion of poorly ventilated lung regions.[156]

Dobutamine does not have a selective action on any vascular bed, and significant metabolic side effects have not been reported. Although it lacks a selective renal vascular effect, dobutamine often enhances urine output by improving cardiac output and thus renal perfusion.[157]

Unlike dopamine, the pharmacologic action of dobutamine does not depend upon releasable stores of norepinephrine.[153] Dobutamine loses its hemodynamic effect during prolonged infusion,[158] presumably because of down-regulation of receptors. Dobutamine maintains a hemodynamic effect much better than dopamine during continuous infusion, since the latter depletes myocardial norepinephrine stores.[159]

a. Pharmacokinetics

A good correlation exists between dobutamine dose, plasma concentration, and hemodynamic effects.[79] In adults, dobutamine is rapidly cleared at a mean rate of 2.34 ± 1.01 $l/min/m^2$ (approximately 60 ml/kg/min) with a plasma half-life of 2.37 ± 0.7 min in patients with congestive heart failure.[81] Similar clearance rates have been reported in a single pediatric study.[80] Both studies also noted moderate interindividual variation in clearance, possibly due to an increased V_d in edematous patients.[79] Dobutamine is metabolized by catechol-*O*-methyl transferase, subsequent glucuronide conjugation, and rapid redistribution from the plasma compartment.

2. Indications and Dose

Dobutamine is indicated in clinical conditions where increased contractility with little effect on peripheral vascular resistance is desired. This setting most often occurs in normotensive patients with congestive heart failure.[155] In patients with congestive heart failure, dobutamine increases stroke volume and cardiac output, while reducing the elevated filling pressure found in this clinical state.[157,160] When used in lower dosages (2 to 10 μg/kg/min), a little change in heart rate is seen.[155] In patients with very poor myocardial function and higher baseline plasma norepinephrine concentrations, however, the effect of dobutamine on cardiac index is attenuated.[161]

In adult patients with myocardial failure and nonobstructed coronary arteries (as expected in pediatric patients), dobutamine improves coronary blood flow and myocardial oxygen supply equal to, or in excess of, the increase in myocardial oxygen demand elicited by its positive inotropic action.[162] Supplementation of myocardial perfusion may partly explain the ability of dobutamine to produce sustained improvement in cardiac function in patients with congestive heart failure following short-term infusions.[163] In one study, a 72-h dobutamine infusion improved endomyocardial ATP to creatinine ratio and the ultrastructural appearance of mitochondria.[164] These and other observations have led to effective intermittent outpatient use of dobutamine in patients with chronic congestive heart failure.[165]

In postoperative cardiovascular surgical patients, dobutamine improves stroke volume and decreases ventricular filling pressures with less positive chronotropy than observed with dopamine.[166] In addition, dobutamine has a more beneficial effect on myocardial blood flow than dopamine.[167] In patients following a heart transplant, myocardial sympathetic innervation is destroyed. Since the inotropic action of dobutamine does not depend on myocardial stores of norepinephrine, it should be a better inotrope than dopamine, and indeed this finding has been observed.[168]

Although dobutamine is an effective inotrope, patients with hypotensive cardiogenic shock may not be improved. Since dobutamine has relatively less peripheral vascular action, dopamine may be superior in this setting.[155,169] Similarly, dobutamine may be disadvantageous in the patient with septic shock and hypotension. Dobutamine should ideally be reserved for septic patients with combined ventricular dysfunction and elevated filling pressures.[155,156]

Based on available pediatric data, dobutamine is a useful inotropic agent in patients with a variety of clinical conditions: cardiovascular failure,[170] following cardiovascular surgery,[171] and septic shock.[172] Clinical studies suggest that dobutamine is most useful in children >12 months of age since the cardiac index in younger patients failed to increase and pulmonary capillary wedge pressure rose in response to 10 μg/kg/min of dobutamine.[172] It is unclear, however, whether the group of children in this study[172] consisted mainly of patients with septic shock or cardiogenic shock; the children with septic shock had elevated cardiac indices and heart rates prior to infusion and, as a group, had a smaller inotropic response to dobutamine. In addition, an unknown quantity of fluid was administered with the dobutamine infusion to maintain preload. It is therefore difficult to conclude whether dobutamine produces a change in myocardial compliance in infants resulting in an increase in pulmonary capillary wedge pressure. In children with heart failure, dobutamine decreases filling pressures.[170,173]

Other age-related effects of dobutamine have been observed. Driscoll and Gillette[173] noted a fairly consistent increase in systemic vascular resistance in children with congenital heart disease contrary to the lowering of systemic vascular resistance observed in adults. Depending on the clinical state, dobutamine-induced increases in cardiac index may be entirely due to elevation in heart rate with little change in stroke volume.[171,174,175] This is noted after open-heart surgery[171,175] and in neonates.[174] Conversely, Schranz and co-workers[170] showed a substantial improvement in stroke volume with little acceleration of heart rate in 12 children with shock from various causes.

Initial infusion rates of dobutamine are 2 to 5 μg/kg/min. Maximal beneficial effects are generally observed with 10 to 15 μg/kg/min and higher infusion rates increase the risk of drug-induced toxicity.[155]

3. Administration and Toxicity

Dobutamine is supplied in 250-mg vials and infusions are prepared as seen in Table 3. As with the other catecholamines, dobutamine should preferably be administered into a central venous site using a continuous infusion pump. Dysrhythmias are the most frequent toxic side effect, although they are less frequently seen than with dopamine or isoproterenol.[176] Other side effects include excessive tachycardia, headaches, anxiety, tremors, and marked increases or decreases in blood pressure.[155]

VI. SUMMARY

The pharmacology of catecholamines has been reviewed in this chapter. These compounds possess potent myocardial and peripheral vascular actions which may be used in pediatric patients to maintain cardiac function, manipulate peripheral and pulmonary vascular tone, and relax bronchial musculature. Optimal use of these potent and useful drugs requires an understanding of their pharmacology and the influence of illness on the hemodynamic actions resulting from their administration. In pediatric applications, age-related changes in drug kinetics or dynamics may occur, further complicating their administration to infants and children. Because of the reasons enumerated above, it is difficult to make firm recommendations about the use of catecholamines in different-aged patients and for different clinical conditions. With these caveats in mind, a table of suggested catecholamine use is provided (Table 2). In the final analysis, the use and dose of each agent should be individually titrated to observed hemodynamic changes.

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Chapter 5

ANTIDYSRHYTHMIC DRUGS IN PEDIATRICS

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TABLE OF CONTENTS

I. Introduction 77

II. Class 1A Agents 79
  A. Quinidine 79
    1. Electrophysiology 80
    2. Pharmacokinetics and Dosage Recommendation 80
    3. Drug Interactions 81
    4. Toxicity 82
  B. Procainamide 83
    1. Electrophysiology 83
    2. Pharmacokinetics and Dosing Recommendations 83
    3. Drug Interactions 84
    4. Toxicity 84
  C. Disopyramide 85
    1. Electrophysiology 85
    2. Pharmacokinetics and Dosing Recommendations 85
    3. Drug Interactions 86
    4. Toxicity 86

III. Class 1B Agents 86
  A. Lidocaine 86
    1. Electrophysiology 86
    2. Pharmacokinetics and Dosage Recommendations 87
    3. Drug Interactions 87
    4. Toxicity 87
  B. Phenytoin 88
    1. Electrophysiology 88
    2. Pharmacokinetics and Dosage Recommendations 89
    3. Drug Interactions 89
    4. Toxicity 89
  C. Tocainide 90
    1. Electrophysiology 90
    2. Pharmacokinetics and Dosage Recommendations 90
    3. Drug Interactions 91
    4. Toxicity 91
  D. Mexiletine 92
    1. Electrophysiology 92
    2. Pharmacokinetics and Dosage Recommendations 92
    3. Drug Interactions 92
    4. Toxicity 93

IV. Class 1C Agents 93

- A. Flecainide 93
  - 1. Electrophysiology 93
  - 2. Pharmacokinetics and Dosage Recommendation 93
  - 3. Drug Interactions 94
  - 4. Toxicity 94
- B. Encainide 94
  - 1. Electrophysiology 95
  - 2. Pharmacokinetics and Dosage Recommendations 95
  - 3. Drug Interactions 95
  - 4. Toxicity 95
- C. Propafenone 95
  - 1. Pharmacokinetics and Dosage 96
  - 2. Toxicity 96

V. Class II Agents 96
- A. Beta Blockers 96

VI. Class III Agents 96
- A. Amiodarone 96
  - 1. Electrophysiology 96
  - 2. Use in Pediatrics 97
  - 3. Pharmacokinetics and Dosage 97
  - 4. Drug Interactions 98
  - 5. Adverse Effects and Toxicity 98
  - 6. Amiodarone Treatment 98
- B. Bretylium 98
  - 1. Electrophysiologic Effects 98
  - 2. Pharmacokinetics and Dosage 99
  - 3. Toxicity 99
  - 4. Drug Interactions 99

VII. Class IV Drugs: Calcium Channel Blockers 99
- A. Electrophysiology 100
  - 1. Verapamil 100
  - 2. Nifedipine 100
  - 3. Diltiazem 100
- B. Pharmacokinetics 101
- C. Dosage 101
  - 1. Verapamil 101
  - 2. Nifedipine 102
  - 3. Diltiazem 102
- D. Drug Interactions 102
  - 1. Verapamil 102
  - 2. Nifedipine 102
  - 3. Diltiazem 102
- E. Toxicity 102

VIII. Digoxin 103
- A. Electrophysiology 103
- B. Pharmacokinetics and Dosing Recommendations 104
- C. Drug Interactions 105

D. ECG Manifestations 105
E. Toxicity 106

IX. Abbreviations 106

References 107

I. INTRODUCTION

Many advances in the detection and treatment of cardiac dysrhythmias have been made over the past several years, and 24-h halter monitoring, exercise stress testing, and programmed electrical stimulation testing have increased our diagnostic capabilities to judge drug efficacy.[1-3a] Much of our knowledge of antidysrhythmic drug efficacy, pharmacokinetics, and toxicity is based primarily on studies in adults. In this chapter we have reviewed the electrophysiology, pharmacokinetics, indications for use, and toxicity of the older and newer drugs as applied to the pediatric population. Where information concerning the use of these drugs in children is lacking, we ask the reader to bear in mind some of the basic differences between children and adults which may affect drug metabolism. These include the increased body water content of the neonate and infant which accounts for the higher volume of distribution (V_d) of drugs seen in infants; GI immaturity in infants less than 6 months of age; reduced plasma protein binding in the newborn and infant; and reduced hepatic metabolism (by P450 enzymes) and renal function in the neonate.[3a]

Also an important consideration in the pediatric population is careful definition of the type of dysrhythmia encountered and then its etiology. Many dysrhythmias of childhood may be self-limited and may not require chronic drug therapy (such as atrial flutter in infants with structurally normal hearts), while others are secondary to congenital heart defects and treatment should focus on repair of the anatomical abnormality.[3b] Also, what might be the treatment of choice for a particular dysrhythmia in adults may not be so in children, depending on the etiology of the dysrhythmia which may confer different electrophysiologic properties requiring a different therapeutic approach.

The classification of antidysrhythmic agents used is a modification of that devised by Vaughan-Williams[4a] (Table 1) and is based on the electrophysiologic properties of the drugs (Table 2). The phases of the action potential of the His-Purkinje system are found in Figure 1. During Phase 0, the gate of the fast sodium channel opens and allows sodium to enter the cell rapidly. During Phase 0, the transmembrane potential rapidly changes from negative to positive. In Phase 1, sodium enters at a reduced rate and marks the beginning of cell repolarization. In Phase 2, the fast channel opens and the slow channel opens causing a plateau in the membrane potential. Potassium exits from the cell during Phase 3. In Phase 4, the ATP-dependent sodium-potassium pump restores the large extracellular sodium and intracellular potassium concentrations.

We have also attempted in this chapter to assess the toxicity of antidysrhythmics, both when used therapeutically and in the event of an overdose. The latter is not an uncommon event and usually occurs when a younger child visits the house of an elderly relative unaccustomed to having exploring youngsters around. Table 3 contains the breakdown of the numbers and types of pediatric exposures of digitalis preparations and antidysrhythmic agents reported to the American Association of Poison Control Centers National Database

TABLE 1
Classification of Antidysrhythmic Agents

Class	Agent	Trade names[a]
1A	Quinidine	
	Sulfate	Cinquin, Quinora®
	Gluconate	Quinaglute®, Duraquin®
	Polygalacturate	Cardioquin®
	Procainamide	Pronestyl-SR®
	Disopyramide	Norpace
1B	Lidocaine	Xylocaine®
	Tocainide	Tonocard
	Phenytoin	Dilantin®
	Mexiletine	Mexitil®
1C	Flecainide	Tambocor®
	Encainide	Encain
	Propafenone	*
	Lorcainide	*
	Indecainide	*
II	Beta blockers	See separate chapter
III	Amiodarone	Cordarone®
	Bretylium	Bretylol®
IV	Calcium channel antagonists	
	Nifedipine	Procardia®
	Verapamil	Calan®, Isoptin®
	Diltiazem	Cardizem®
V	Digoxin	Lanoxin®

Note: Asterisk indicates investigational agents.

[a] Other trade names are available for these drugs.

Modified from Vaughan-Williams, E. M., *J. Clin. Pharmacol.*, 24, 129, 1984. With permission.

TABLE 2
Classification of Antiarrhythmic Agents

Group	Membrane-depressant activity	Actions		Extracardiac action
		Effect on action potential duration	Sympatholytic effect	
Class IA	Strong	Lengthen	None	Anticholinergic
Class IB	Strong	Shorten	None	Anticholinergic and anticonvulsant
Class IC	Strong	None	None	Not relevant
Class II	Weak	Shorten	Strong	Not relevant
Class III	None	Lengthen	B, neuron blockade A, noncompetitive	B, not relevant A, coronary dilator
Class IV	Phase 4 only for verapramil	None	Noncompetitive	Coronary dilator

Note: B, bretylium; A, amiodarone.

Modified from Singh, B. N. and Hauswirth, O., *Am. Heart J.*, 87, 367, 1974. With permission.

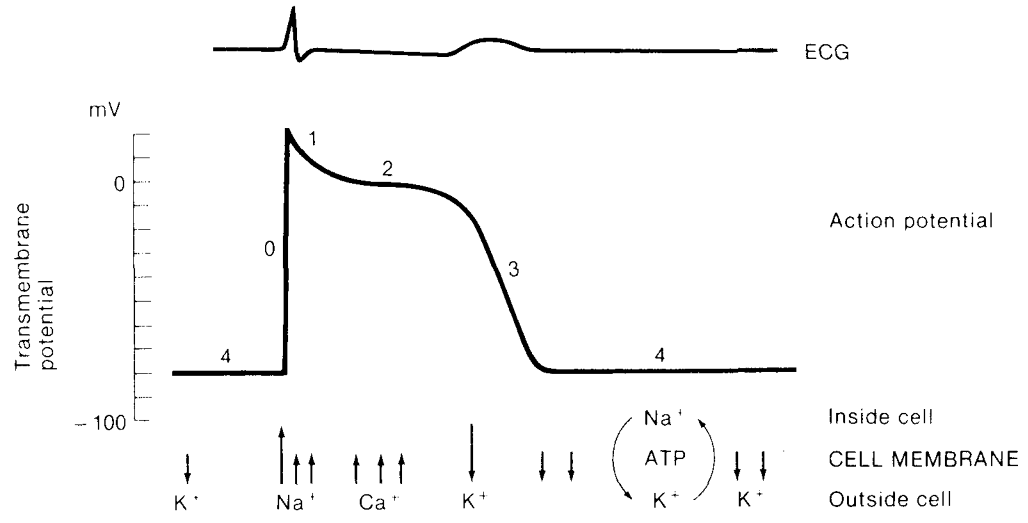

FIGURE 1.. Myocardial cell action potential.

TABLE 3
Number, Age Distribution, and Severity of Intoxications of Cardiac Glycosides and Antidysrhythmic Agents

Reported to AAPCC Data Base, 1984—1986 (Based on 2,729,631 Total Exposures)

		Age (years)			Severity of intoxication					
	Total	**<6**	**6—17**	**>17**	**None**	**Min**	**Mod**	**Maj**	**Death**	**(%)**
Cardiac glycosides	3156	1748	213	1145	1678	471	202	176	23	
	(0.12%)	(55.4%)	(6.7%)	(36.3%)						(0.7%)
Antidysrhythmics	1844	577	134	1069	874	353	91	79	17	
	(0.06%)	(31.3%)	(7.3%)	(57.9%)						(0.9%)
Calcium channel	2557	1219	132	1146	1392	434	102	83	12	
blockers	(0.09%)	(47.7%)	(5.2%)	(44.8%)						(0.5%)

Note: AAPCC, American Association of Poison Control Centers; Min, minimal toxicity; Mod, moderate toxicity; and Maj, major toxicity.

from 1984 to 1986.[4b,c] The general management principles of antidysrhythmic intoxications involve (1) establishing vital functions and administering supportive care as needed and (2) gastrointestinal (GI) decontamination generally consisting of activated charcoal and cathartics within 4 h postingestion. Vomiting induced by ipecac syrup may stimulate vagal reflexes and worsen bradysrhythmias. Generally we do not recommend this for acute overdoses of these agents. Before insertion of a gastric tube for lavage, it is important to perform an electrocardiogram (ECG) to ensure no dysrhythmias are present and to monitor the ECG while inserting the tube when these agents are ingested. Initial and repeated doses of activated charcoal every 3 to 6 h may enhance the elimination of certain antidysrhythmic agents like digoxin or quinidine and are recommended. Specific therapies of overdose and poisonings will be discussed under each class of drugs.

II. CLASS 1A AGENTS

A. QUINIDINE

Quinidine, a dextrorotatory isomer of quinine, is a Class 1a antidysrhythmic agent which is used in children for the treatment of both supraventricular (SVT) and ventricular tachycardias.[3a] It is very commonly used with digoxin in the treatment of atrial flutter and fibrillation. Because of the toxicity of quinidine, it is recommended only after other appropriate agents have been tried. Quinidine has central effects on conductivity and excitability and peripheral anticholinergic and vasodilatory effects.

1. Electrophysiology

The dominant electrophysiologic effect of quinidine and the other Class 1A antidysrhythmic agents is to block the fast inward sodium current (i.e., to decrease the rate of rise of Phase 0 during depolarization of the cardiac membrane.[1] This decrease in membrane permeability to sodium results in a decrease in V_{max} and a prolongation of the action potential duration (APD) and effective refractory period (ERP) in atrial, ventricular, and Purkinje fibers.[2] Quinidine exerts a *direct* effect at the sinoatrial (SA) node and especially the atrioventricular (AV) node, prolonging the ERP and APD.[3a] This effect may be dangerous in patients with decreased conduction and low vagal tone, since it can lead to a serious AV block. Quinidine as well as the other Class 1A drugs also exerts an *indirect* vagolytic (anticholinergic) effect which can enhance conduction through the AV node. This effect may be dangerous in atrial flutter where quinidine might slow the atrial rate directly, but indirectly enhance AV conduction velocity and allow for a 1:1 AV conduction.[5a] At therapeutic doses, the direct effect predominates. For this reason, it has been suggested that digoxin be initiated before quinidine in the treatment of atrial flutter and fibrillation.[3a] When using quinidine and digoxin concommitantly, digoxin levels should be monitored carefully (see quinidine drug interactions).[24,26]

Quinidine should be used with caution in children with the potential for sick sinus syndrome (e.g., children who have undergone the Mustard operation or other atrial operations), since quinidine can suppress the sinus node causing extreme bradycardia and possibly sudden death.[5b] It is recommended that children with the potential for the sick sinus syndrome receive a pacemaker before treatment with any drugs which can suppress sinus node function (e.g., quinidine, procainamide, disopyramide, β-blockers, verapamil, and amiodarone).[5b,6]

2. Pharmacokinetics and Dosage Recommendations

Quinidine is available in three salt forms: sulfate, gluconate, and polyglucuronate. The sulfate form is more rapidly absorbed than the other two, reaching peak levels in 1 to 2 h vs. 3 to 5 h for the gluconate form.[9,10] The slower absorption of the gluconate and the glucuronate salts of quinidine allows for less frequent dosing of the drug: two to three times daily for the gluconate vs. four to six times daily for the sulfate (Table 4).

The disposition kinetics of quinidine has been described by a two-compartment model, with the distribution phase occurring in approximately 7 min and the half-life of elimination occurring in 6.3 h.[11] This elimination half-life is in agreement with the half-lives reported by several authors, all ranging on average from 6 to 8 h.[11,13] This range of half-lives in adults contrasts with the elimination half-life of 4 to 5 h seen in children.[14,15] Quinidine is highly protein-bound in older children and adults (80 to 90%). In children, however, Pickoff and colleagues[16] found a decrease in protein binding with age. In neonates, infants, and children (with cyanotic congenital heart disease), free quinidine levels of 39, 21, and 14%, respectively, were found.[16] Since plasma clearance of quinidine has been significantly correlated with the level of unbound quinidine in plasma,[3,17] the higher levels of unbound quinidine found in younger children may account for the need for relatively higher doses and/or more frequent dosing of quinidine in children to maintain therapeutic blood levels.

Quinidine is eliminated primarily by the liver (60 to 85%) with renal elimination accounting for only 15 to 40%.[13] Several quinidine metabolites (3-hydroxyquinidine, 2′-quinidinone, *O*-desmethylquinidine, and quinidine-*N*-oxide) have been identified with phar-

TABLE 4
Clinical Use and Pharmacokinetics of Class 1A Antidysrhythmic Drugs

Dosage	Quinidine	Procainamide	Disopyramide
Oral (mg/kg/24 h)	15—60 mg/kg 10 (>12 years) 15 (<12 years)	15—50 (children)	10—30 (>1 years) 10—20 (1—4 years) 10—15 (4—12 years) 6—15 (12—18 years)
Dosing interval	q 6 h	q 4—6 h	q 4—6 h
Intravenous	Not recommended	1 mg/kg q 5 min to max of 10mg/kg 20—50 μg/kg/min infusion	Not available for intravenous use in adults
Blood levels			
Therapeutic	1—5 μg/ml[a]	4—10 μg/ml	2—6 μg/ml
Toxic	>5 μg/ml[b]	>8—10 μg/ml	>9 μg/ml (toxic) >4—5 μg/ml can be toxic in some patients
Pharmacokinetics			
Absorption	75—85%	75—95%	80—90%
Peak plasma concentration	1—2 h (sulfate) 3—5 h (gluconate)	1—2 h	0.5— 3 h
Half-life elimination	4.6 h (children) 6—6.5 (adults)	13.5 h (neonate)[a] 1.7 h (children) 2.2—4.7 h (adults)	4.8 h (children) 4—10 h (adults)
Protein binding	80—90% (adults)	15%	50—70%
V_d	3 l/kg	2.2 l/kg (children)	1.0 l/kg (adults)
Elimination	Hepatic, 60—85% Renal, 15—40%	Hepatic, 50% metabolized to NAPA Renal, 50% excreted unchanged	Renal, 50% excreted unchanged
Clearance	0.383 l/h/kg (children)	19 ml/min/kg (children)	1.5 ml/kg/min (adults)

[a] Using specific assays.
[b] Great variability among patients.

macologic activity similar to that of the parent compound.[13] These metabolites probably make a significant contribution to the overall effect of quinidine.

The recommended oral dose of quinidine in children is 15 to 60 mg/kg up to 600 to 900 mg a day divided into four doses daily.[3a,22] If a sustained-release form such as Quinaglute® or Cardioquin® is used, Szefler and colleagues[15] recommend 15 mg/kg/d in children less than 12 years of age (q 8 to 12 h) and 10 mg/kg/d in children greater than 12 years of age in divided doses every 8 to 12 h. In neonates the suggested dose is 4 to 10 mg/kg p.o. every 6 h, to be discontinued if the QRS interval is greater than 0.10 s.[23] The intravenous route of administration is contraindicated in children. Electrocardiographic effects of quinidine are prolongation of PR, QRS, and QT intervals.

The therapeutic range of plasma quinidine concentration for treatment of atrial and ventricular dysrhythmias in adults is approximately 1 to 5 μg/ml.[18,21] There are few data in the literature to form a definitive range for quinidine in children. The serum quinidine level reported reflects total serum quinidine (bound and unbound), and in younger children the fraction of free quinidine may be significantly increased. In children, as in adults, great interindividual variability exists regarding the level of quinidine that will be therapeutically effective. So, as always, we monitor clinically for signs of toxicity.

3. Drug Interactions

One of the most significant drug interactions is that of quinidine and digoxin. Concomitant use of quinidine and digoxin can result in a two- to threefold increase in the serum digoxin concentration.[24,26] This effect has been found to occur in patients with a serum quinidine level of 2 μg/ml or greater.[27] In the latter study, the increase in digoxin was seen within a few hours of starting quinidine therapy; however, a steady-state serum digoxin level may not be reached for several days or weeks.[26,27] In patients receiving quinidine and verapamil concomitantly, serum quinidine levels should be monitored closely since verapamil can cause a 25 to 50% decrease in quinidine clearance.[28,29] Also, hypotensive episodes have occurred in patients receiving quinidine and intravenous verapamil.[30] The use of hepatic enzyme-inducing drugs such as phenytoin, rifampin, and phenobarbital with quinidine has been noted to decrease serum quinidine probably secondary to increased metabolism.[31,32] Quinidine, when used with neuromuscular blocking agents, causes an increase in neuromuscular blockade.[33] Koch-Weser[34] found an increased anticoagulant effect when quinidine was used by patients on chronic warfarin therapy. The latter effect is probably due to displacement of warfarin from its protein binding sites.[35] Further, 11 patients on chronic quinidine who had amiodarone added to the regimen showed an increase in their serum quinidine levels.[38] A 37% decrease in quinidine dose was necessary to maintain a stable (preamiodarone) plasma level of quinidine.[38] An increase in urine pH from 6 to 7 will decrease renal clearance of quinidine by as much as 50%.[36]

4. Toxicity

Some of the adverse electrophysiologic effects of quinidine (ventricular dysrhythmias, sinus node depression, and AV block) were mentioned previously. Of particular concern with quinidine use is the frequent occurrence (0.5 to 4.4%) of a syndrome manifested by light-headedness and syncope; it can result in sudden death called "quinidine syncope".[8,109] This syndrome, which carries a 12% mortality, is associated with ventricular dysrhythmias, especially torsades de pointes, a polymorphic ventricular tachycardia, preceded by marked QT interval prolongation.[109] Quinidine syncope can develop after just one dose of quinidine or with low or therapeutic drug levels and most frequently occurs when quinidine is used to terminate or prevent atrial flutter or fibrillation, especially when digoxin is used concomitantly.[7,8,109] Torsades de pointes may occur apart from the syndrome of "quinidine syncope" when blood levels of quinidine exceed the therapeutic range or other signs of toxicity exist and is often accompanied by hypokalemia.[8,106] Should a child develop quinidine-induced torsades de pointes, quinidine should be withdrawn immediately, hypokalemia should be corrected for, and if necessary maneuvers should be made to increase heart rate (administration of isoproterenol or cardiac pacing).[8] Because of the potentially life-threatening dysrhythmias which can result upon initiation of quinidine therapy (e.g., sick sinus syndrome, torsades de pointes), it has been recommended that children be hospitalized when starting quinidine treatment.[5,8]

In a study of 652 patients receiving quinidine (122 patients receiving quinidine alone), in decreasing order of frequency, the adverse reactions included GI symptoms (7.8%), cardiac dysrhythmias (2.5%), fever (1.7%), dermatologic reactions (0.9%), cinchonism (0.9%), and hemolytic anemia (0.2%).[36] In addition, quinidine has been associated with respiratory depression and arrest,[45] convulsions and coma,[45,46a] systemic acidosis and hypoglycemia, and, in glucose-6-phosphate dehydrogenase-deficient patients, hemolysis.[22,47] Quinidine-induced thrombocytopenia on an autoimmune basis has been reported.[46b]

Treatment of intoxication due to agents in this group is largely symptomatic.[47] Both mild alkalemia and hypokalemia have been found to be somewhat protective. Hypotension should be treated with intravenous fluids. Dysrhythmias should be treated with lidocaine or phenytoin, which will decrease the action potential, duration, and refractory period. The use of other type Ia agents is contraindicated. Bretylium should be used with caution because of synergistic AV nodal suppression. Isoproterenol infusion and overdrive pacing may be needed to treat a typical ventricular tachycardia. Forced diuresis has not been consistently effective and this is no longer recommended.[48] Hemodialysis would not be indicated unless renal failure exists.[49,50]

B. PROCAINAMIDE

Procainamide has been effective in (1) the treatment of atrial extrasystoles, paroxysmal supraventricular tachycardias, atrial fibrillation, ventricular extrasystoles, and tachycardias and (2) in preventing recurrence of atrial flutter and fibrillation following cardioversion. Procainamide is also effective in controlling the ventricular response in patients with the Wolff-Parkinson-White (WPW) syndrome complicated by atrial flutter or atrial fibrillation.[49]

1. Electrophysiology

Procainamide shares many of the same electrophysiologic characteristics of quinidine.[53] Arrhythmic actions are similar to quinidine, but the anticholinergic, vasodilatory, and negative inotropic effects of procainamide are less. Procainamide may (1) worsen sinus node or AV dysfunction, (2) cause torsades de pointes, and (3) through an indirect vagolytic effect (not as pronounced as that of quinidine or disopyramide) increase AV node conduction.[2,4,54-56] When premature depolarizations result from a reentry mechanism, procainamide-induced slowing of conduction along a depressed segment of reentry loop can convert an area of unidirectional block to bidirectional block, thus abolishing the arrhythmia.[2,35]

In patients with atrial flutter or fibrillation complicating the WPW syndrome, procainamide has been effective in lengthening the effective refractory period of the accessory pathway (in the anterograde direction), especially in patients with an ERP of 270 ms or greater.[51,52] However, in patients with an ERP of 270 ms or less, and hence the group at greatest risk of achieving dangerously high ventricular rates if atrial fibrillation supervenes, Wellens and colleagues[52] found that procainamide and quinidine gave no significant lengthening of the ERP. Only amiodarone produced a significant increase in duration of ERP in this latter group of patients. Hence, before starting procainamide treatment, electrophysiologic studies measuring ERP are appropriate in patients with WPW syndrome and atrial flutter-fibrillation. Procainamide like quinidine increases the PR, QRS, and QT intervals,[50] although the effect on the QT and QRS is not as marked as it is with quinidine.[2]

N-Acetyl procainamide (NAPA), an active metabolite of procainamide, does not share the same electrophysiologic properties as its parent compound.[70] NAPA prolongs atrial and ventricular refractoriness, but has little effect on His-Purkinje conduction.[54,55] It has been suggested that if a patient's therapy is changed from procainamide to NAPA, the therapeutic efficacy of NAPA should be established since the efficacy of NAPA differs from that of procainamide.[55,56] NAPA-like procainamide has been associated with the dangerous ventricular dysrhythmia of torsades de pointes.[57,58] As with other antidysrhythmics associated with torsades de pointes, the presence of marked QT interval prolongation (greater than 0.56 s) appears to be the major predisposing factor to its development.[57,58] Patients on procainamide who are fast acetylators or who have renal impairment may achieve dangerously high levels of NAPA and thus place themselves at greater risk of developing this fatal dysrhythmia.[57]

2. Pharmacokinetics and Dosing Recommendations

Approximately 75 to 95% of procainamide is absorbed following oral administration and 15% of the drug undergoes first-pass hepatic elimination.[62,63] In the liver, procainamide is metabolized to *N*-acetylprocainamide by the enzyme *N*-acetyl transferase. The activity of the enzyme is polymodally distributed, with half of the patients being slow acetylators and half being fast acetylators, eliminating 12 and 23% of orally administered procainamide dose as NAPA, respectively.[4,64] Only 15% of the drug is protein-bound.[3,4] In children the drug is rapidly distributed (approximately 10 min) and rapidly cleared with an elimination half-life of 1.7 h.[65] In adults, however, procainamide is eliminated more slowly, with an elimination half-life of 2.2 to 4.7 h.[62,63,66] In children as in adults, the elimination of procainamide can be significantly altered in renal insufficiency, since as much as 50% of the administered dose of procainamide appears unchanged in the urine.[68] Gibson et al.[68] found a 11- to 16-h increase in the elimination half-life of procainamide in adult patients with renal failure. Proper dosing of procainamide can be difficult in patients with renal failure also because elevated plasma procainamide levels can lead to markedly elevated plasma levels of NAPA, which has a half-life of elimination twice that of procainamide (6 to 8 h vs. 3 to 4 h).[59] In renal disease, it may be impossible to achieve therapeutic procainamide levels without concomitant toxic elevation of the plasma NAPA levels.[4a,b]

To the best of our knowledge, there is only one case report of the elimination kinetics of procainamide in a child less than 7 years of age and this was documented in a neonate born to a mother receiving procainamide treatment prior to birth.[67] In this child, the elimination half-life for procainamide was 13.5 h and for NAPA it was 19.5 h.

The recommended daily oral dose of procainamide for children is 15 to 50 mg/kg given in divided doses each every 4 to 6 h.[3a] For adults the recommended daily dose is 50 mg/kg (of sustained-release procainamide) given in divided doses every 6 h.[69] In children the initial intravenous dosage may be 1 mg/kg every 5 min to a maximum of 10 or 3 to 6 mg/kg over 5 min[3a] and then intravenous maintenance at a 20 to 50 μg/kg/min infusion. The intramuscular route of administration offers no advantage over the oral route.[35] Procainamide is the standard Class 1A drug for intravenous use.

The effective therapeutic concentration range for procainamide is 4 to 10 μg/ml, with an early toxicity beginning at 8 to 10 μg/ml.[21] Some patients may respond to higher concentrations without experiencing toxicity.[21,70] However, plasma levels greater than 16 μg/ml have been associated with hypertension, atrioventricular or intraventricular conduction disturbances, ventricular dysrhythmias, and cardiac arrest.[3a,70] The therapeutic concentration range from NAPA is probably greater than 10 μg/ml with toxicity occurring over a wide range (10 to 40 μg/ml).[21]

3. Drug Interactions

Drug interactions have not been a major problem with procainamide therapy.[4a] Some interactions include increased procainamide toxicity when procainamide is administered with amiodarone (mechanism unknown),[38] cimetidine (due to increased renal excretion),[71] and ranitidine.[72,73] Additive depression of AV conduction may occur when procainamide is given to patients with digoxin toxicity.[4a] A syngergistic depressant effect on cardiac contractility may occur when procainamide and lidocaine are given concomitantly, a concern especially in the coronary care unit.[4a,74]

4. Toxicity

The major adverse cardiac effects of procainamide include hypotension, decreased cardiac output, asystole, AV block, and ventricular tachycardias, including torsades de pointes (Table 3).[3a,54,60] Like quinidine, many of the toxic cardiac effects of procainamide are manifested by progressive QT and QRS interval lengthening.[35] However, the incidence of sudden death or recurrent syncope due to ventricular tachycardia (especially torsades de pointes) is greater with quinidine use.[8,35,54]

Procainamide use has been associated with the development of a lupus erythematosus-like syndrome in as many as 30 to 40% of patients.[75,76] The syndrome may appear (1) as early as 2 weeks after initiation of therapy, (2) is more likely to occur in slow acetylators of procainamide, and (3) is not associated with NAPA.[4a-c,35,76] Chronic administration of procainamide (and especially toxic doses) has been commonly associated with anorexia, nausea, vomiting, and diarrhea.[35] Rarely has agranulocytosis been associated with procainamide use.[78]

C. DISOPYRAMIDE

Disopyramide is similar to quinidine in its antiarrhythmic action; however, it has greater depression on the myocardium and more anticholinergic activity, as well as peripheral vasoconstrictor action. It may precipitate or worsen heart failure. In adults disopyramide has been successfully used in the treatment of supraventricular dysrhythmias,[79] ventricular premature beats,[79-82] and ventricular tachycardias[83] and in the control of ventricular responses in patients with the WPW syndrome associated with atrial flutter-fibrillation.[84] In children disopyramide has been used in the treatment of supraventricular ventricular tachycardias.[85-87] Hordof and collegues found it particularly useful in the treatment of recurrent ventricular dysrhythmias.[87] In six of eight patients (10 to 18 years) receiving disopyramide for control of ventricular dysrhythmias, excellent control of the dysrhythmia was achieved using an average of 11 mg/kg/d of the drug.

1. Electrophysiology

The electrophysiologic effects of disopyramide are similar to those described for quinidine and procainamide.[85-87] Disopyramide acts like quinidine on the AV node.[88,89,92,93] For this reason, patients with atrial fibrillation or flutter should be digitalized prior to disopyramide use.[69]

Disopyramide, when used in upper therapeutic-toxic doses and under cholinergic blockade, was shown to have a direct depressant effect on normal nodal cells.[94] The sick sinus syndrome may well be a contraindication and would require a pacemaker prior to Class 1A drug therapy.[6] Disopyramide has proven effective in patients with WPW syndrome complicated by atrial flutter-fibrillation.[84,92] Disopyramide can cause torsades de pointes in patients receiving the usual therapeutic doses.[109]

2. Pharmacokinetics and Dosing Recommendations

Disopyramide is available in the oral form as standard capsules or as controlled-release tablets.[96] It is approximately 80 to 90% bioavailable,[95,97] with a small percentage undergoing first-pass metabolism in the liver to the active mono-*N*-dealkylated metabolite (MND).[4a] Peak concentrations are seen 0.5 to 3 h after a dose and the elimination half-life is 4 to 10 h with a mean of 6.7 h in normal adult subjects.[96,97] This half-life of elimination contrasts with the half-life of 4.8 h noted in children.[87] Disopyramide is eliminated primarily by the kidneys, with 50% of the drug excreted unchanged and 20% excreted as the *N*-dealkylated metabolite.[96,100] The dose of the drug should be adjusted in patients with renal disease since an elimination half-life of 6.2 to 43 h was reported in patients with elevated creatinine clearances.[96,100] A wide range of protein-binding of disopyramide has been reported (50 to 95%).[100-102] The protein-binding of disopyramide and its metabolite MND have been shown to be concentration dependent.[102,103] As the total disopyramide concentration increases, there is a progressive increase in the fraction of free disopyramide and MND.[102,103] However, within the therapeutic range of 2 to 6 μg/ml, about 50 to 70% of the disopyramide are bound to protein.[35]

The recommended daily doses of disopyramide for children are listed in Table 1. These dosages are much in excess of the 5 to 7 mg/kg needed in adults to attain plasma disopyramide levels in the therapeutic range of 2 to 4 μg/ml.[3a] The longer elimination half-life in children probably accounts for the higher dosages needed in children.

The generally accepted therapeutic plasma drug range of disopyramide is approximately 2 to 6 μg/ml.[21,96] However, adverse effects have been seen within the therapeutic range.[104,105] Martin and colleagues[104] noted a deterioration in left ventricular function (as documented by echocardiography) in four adult patients with plasma disopyramide levels ranging from 1.5 to 5.0 μg/ml.

3. Drug Interactions

Disopyramide should be used with extreme caution with beta-adrenergic blockers, since the additive effects of these drugs on contractility and blockade of compensating reflexes could precipitate cardiac failure.[106] Use of disopyramide with warfarin results in an increased anticoagulant effect due to decreased warfarin metabolism.[107] Concomitant use of procainamide with phenytoin and rifampin can result in a decreased disopyramide effect due to increased disopyramide metabolism.[108]

4. Toxicity

In addition to some of the adverse cardiac effects mentioned in the section on electrophysiology (depression at the sinus node, vagolytic effect at the AV node, and torsades de pointes), disopyramide exerts a negative inotropic effect which along with its vasoconstrictor properties can exacerbate heart failure.[111] To reduce the risk of cardiac decompensation with the use of disopyramide, it has been suggested that:

1. Loading doses of disopyramide be avoided
2. Maintenance dosages of the drug be reduced in the setting of renal insufficiency
3. Dose titrations be done gradually
4. Patients with decompensated heart failure or significant left ventricular failure be omitted from disopyramide treatment[112]

The majority of noncardiac side effects of disopyramide are related to its anticholinergic activity and include dry mouth, urinary hesitancy, constipation, blurred vision, and dry eyes, nose, and throat.[80] Uterine contractions, glaucoma, cholestasis, hypoglycemia, and psychosis have also been reported.[4a]

III. CLASS 1B AGENTS

A. LIDOCAINE

The Class 1b antidysrhythmic agents, which are comprised of lidocaine, its analogs mexiletine and tocainide, and phenytoin, all act by shortening cardiac repolarization (i.e., the QT interval). Lidocaine is considered the drug of choice for emergency intravenous treatment and prevention of ventricular dysrhythmias, including ventricular fibrillation,[113,126] especially in the setting of an acute myocardial infarction, general and cardiac surgery, congestive heart failure, and digitalis intoxication. Lidocaine has little effect on conduction, atrial function, myocardial contractility, or blood pressure in therapeutic doses. It is the drug of choice for initial therapy of most ventricular tachyarrythmias.[35,110,117,134] Lidocaine is relatively devoid of toxic side effects and effective plasma concentrations can be achieved quickly by intravenous titration.[35] It is relatively ineffective in the treatment of supraventricular dysrhythmias.[115,116]

1. Electrophysiology

Lidocaine exerts its antidysrhythmic effect in tissues exhibiting a long APB, i.e., ventricular muscle and Purkinje fibers.[3a] In Purkinje fibers, lidocaine acts by depressing V_{max}, the AP amplitude, conduction velocity, and membrane responsiveness. These effects are greatest at higher potassium levels and become minimal or absent at potassium levels less than 3 meq/l.

The electrophysiologic action that contributes most to the effectiveness of lidocaine in the treatment of ventricular dysrhythmias is blockade of active and inactive sodium channels in Purkinje fibers and ventricular cells, thus shortening the action-potential duration, depressing abnormal automaticity of Purkinje cells and diastolic depolarization.[2] It suppresses the activity of depolarized arrythmic tissue while *minimally* interfering with the electrical activity of normal tissue, thereby suppressing arrhythmias associated with depolarization such as ischemia and digitalis toxicity. Lidocaine is ineffective in arrhythmias in normally polarized tissues.

Lidocaine has been shown to be partially effective in the prevention of ventricular fibrillation following an acute MI (myocardial infarction).[117,118] In a study, none of 107 patients given lidocaine within 6 h of an acute MI developed ventricular fibrillation, whereas 9 of 105 similar patients receiving placebo did.[117] Lidocaine in therapeutic concentrations has little effect on AV conduction[119] or SA node conduction.[114] In diseased hearts, however, lidocaine has been associated with depressed sinus node function and AV block.[120,121]

2. Pharmacokinetics and Dosage Recommendations

The oral bioavailability of lidocaine is very low (35 to 40%) due to extensive first pass elimination in the liver.[122] Approximately 60 to 80% of lidocaine are protein bound and the degree of protein binding is determined largely by the concentration of the acute reactant alpha-1 acid glycoprotein.[132] The disposition kinetics of intravenously administered lidocaine follows a two-compartment model with an alpha-phase elimination half-life of 8 to 10 min and a beta-phase half-life of 65 to 138 min.[122] Because of this short half-life of 1.5 h, the intravenous route of administration of lidocaine is necessary to maintain therapeutic plasma levels of lidocaine. The volume of distribution of lidocaine is 1.3 l/kg, with a clearance of 10 ml/min/kg. Less than 3% of lidocaine is excreted unchanged in the liver. Two pharmacologically active metabolites of lidocaine, monoethylglycine xylidide metabolite (MEGX) and glycine xylidide, have been identified.[133] MEGX has convulsant properties.

Lidocaine kinetics is unaffected in renal disease.[12] However, severe hepatic failure may result in a 40 to 50% reduction in the lidocaine elimination rate and CHF may result in a 50% reduction in the V_d, necessitating in both disease states a proportionate reduction in the lidocaine infusion rate. Also, of particular concern in children, patients with right to left intracardiac shunting (as may occur in Tetralogy of Fallot) may experience an 18 to 38% rise in lidocaine levels due to decreased lidocaine uptake in the lungs.[131] Therefore a proportionate reduction in lidocaine infusion rate is appropriate in this setting.

The dosage recommendation for intravenous lidocaine for children is a loading of 1 mg/kg per dose given every 5 to 10 min until the desired effect or a maximum total dose of 5 mg/kg is obtained, followed by a continuous intravenous drip of 10 to 50 μg/kg/min.[3a,22] The infusion rate will depend on the desired plasma level of lidocaine and the clearance of the drug. With an average clearance of 10 ml/min/kg and a desired lidocaine level of 4 μg/ml, a continuous infusion of 40 μg/kg/min is necessary. In CHF the rate would be halved since the clearance of lidocaine in this setting is halved. The therapeutic concentration range for lidocaine is 1.5 to 5.5 μg/ml, with toxicity beginning at 5.0 μg/ml.[21]

3. Drug Interactions

Propranolol, when administered with lidocaine, lowers the clearance of the drug (possibly due to decreased hepatic flow and enzyme inhibition), thus increasing lidocaine levels and toxicity. The metabolism of lidocaine may also be decreased with concomitant use of cimetidine.[128] Bupivacaine has been shown to displace protein-bound lidocaine, thus increasing plasma levels of the drug.[129] Finally, concomitant use of tocainide with lidocaine may result in seizures.[130]

4. Toxicity

In addition to some of the adverse cardiac effects mentioned previously (acceleration of the ventricular response in WPW syndrome, depressed sinus node function, and AV block), lidocaine may produce heart block, especially in patients with preexisting long His-Purkinje conduction time.[121] In patients known to have advanced sinus node dysfunction or prior AV block, insertion of a temporary ventricular pacemaker should be considered since such patients depend on escape rhythms to maintain their cardiac output. In general, clinically significant adverse hemodynamic effects are rare.[35,110]

Toxic effects may occur within the therapeutic range; however, most commonly occur above 5 μg/ml.[21] The toxic effects of lidocaine are predominantly limited to the CNS and include somnolence, vertigo, disorientation, psychosis, paresthesis, muscle twitching, and rarely respiratory depression and seizures.[110] The incidence of neurologic toxicity associated with chronic lidocaine use is 4.1% (31 of 750 patients), with 6 of the 31 patients manifesting life-threatening toxicity.[110,134] The most serious toxicity occurs at concentrations greater than 9 μg/ml and may include decreased cardiac output, hypotension, muscle twitching, convulsions, and respiratory arrest.[135] Methemoglobinemia has been documented during topical lidocaine use.[136]

Therapy for lidocaine intoxication focuses on the treatment of seizures and methemoglobinemia.[47] Seizures may be relatively refractory to therapy. Diazepam is the drug of choice, followed by phenobarbital if needed. Avoid phenytoin because of its synergistic cardiac effects. Because both lidocaine and its metabolite, monoethylglycine xylidide (MEGX), may cause convulsions, the potential for seizures may remain even after the lidocaine serum concentration falls below 5 μg/ml. Methylene blue and oxygen should be administered if the methemoglobin level is >30% and is accompanied by dyspnea, metabolic acidosis, or altered mental status. Hemodialysis is ineffective.

B. PHENYTOIN

Phenytoin has been most useful in the pediatric population for the treatment of ventricular dysrhythmias, especially those which occur postoperatively or as a result of digitalis toxicity.[47,138a,139] Phenytoin in combination with propranolol is also beneficial in controlling ventricular tachycardia in patients with the prolonged QT interval syndrome.[138a] Its usefulness in reversing cardiac conduction abnormalities in tricyclic antidepressant overdose has not been confirmed.[138b]

1. Electrophysiology

Phenytoin, like lidocaine, depresses automacity in both ventricular and atrial tissues, depresses phase 0 and the fast response, and shortens the APD and ERP. Phenytoin acts predominantly on the Purkinje fibers with minimal effect on other cardiac tissue.[140] The action of phenytoin at the Purkinje fibers is highly dependent on the plasma potassium concentration, the phenytoin concentration, and whether the tissue is ischemic or not.

At low potassium concentration (less than 3 meq/l), a low phenytoin level (1 to 3 μg/ml) may increase (make more negative) the resting membrane potential, the V_{max} of phase 0, and the AP amplitude of both atrial and Purkinje fibers.[140] These effects may explain the beneficial response seen in digitalis-induced reentrant dysrhythmias.[2,140] Toxic levels of digoxin can cause a decrease in the V_{max} and AP amplitude, resulting in slowed conduction and unidirectional block, a set-up for a reentrant dysrhythmia. Phenytoin, by increasing conduction velocity in the retrograde direction, may allow an impulse to cross the area of block quickly enough so that it encounters ventricular fibers that have yet to repolarize, hence breaking the reentrant circuit.[140]

As potassium levels are increased (to the therapeutic range of 4 to 5 meq/l), low levels of phenytoin (1 to 3 μg/ml) result in just a slight increase in the resting membrane potential, V_{max}, and AP amplitude. In contrast, higher levels of phenytoin (5 to 20 μg/ml) in the presence of normal potassium levels result in a decrease in the resting membrane potential, AP amplitude, and V_{max} of phase 0 and may slow conduction velocity.[137] Phenytoin decreases the slope of phase 4 depolarization of Purkinje fibers (thus suppressing automaticity in the Purkinje fibers) and it suppresses delayed after-depolarizations induced by digitalis in Purkinje fibers.[141]

2. Pharmacokinetics and Dosage Recommendations

In general, the oral bioavailability of phenytoin is high (80 to 95%); however, absorption is significantly decreased during the first 2 weeks of life because phenytoin, a weak acid (pKa of 8.3) is almost totally ionized in the neutral gastric pH of the neonate and hence poorly absorbed through the lipophilic GI membrane.[3a] By 6 months, the infant's GI system has matured sufficiently to achieve adult absorption levels of phenytoin. Concomitant ingestion of antacids and activated charcoal diminishes absorption of phenytoin while food enhances it. In adults the time of peak plasma concentration of phenytoin is dose related and ranges from 8 to 32 h.[143]

A total of 90 to 95% of phenytoin is protein bound, mostly to albumin. Protein binding of phenytoin is decreased in renal failure, hypoalbuminemia, nephrotic syndrome, hyperbilirubinemia, and diabetes. With the use of certain drugs which displace phenytoin from its binding sites, such as salicylates, valproic acid, sulfonylureas, and phenylbutazone, binding is also reduced.[35,110,146-148] Plasma phenytoin binding is reduced in the neonate and may not reach adult levels until 3 months of age.[149]

Phenytoin is infused until (1) a therapeutic response is seen, (2) toxic side effects occur or (3) a full loading dose is administered. An intravenous phenytoin protocol for rapid loading of the drug in children with ventricular dysrhythmias has been devised by Garson and Gillette.[152] Over 1 h, 15 mg/kg are given intravenously. Every 5 min, 1/13 of the total dose is pushed undiluted and cleared from the tube with normal saline. Concomitantly, oral phenytoin is begun with 3 mg/kg, followed in 6 h by 2 mg/kg, and followed finally in 6 h by maintenance oral phenytoin of 2.5 to 3.0 mg/kg every 12 h. This protocol is inappropriate for patients with cardiac decompensation because of the high risk of a hypotensive episode and should be given with caution (i.e., slowly) in patients with abnormal hemodynamics. Once a certain level of phenytoin has been achieved with a known dose of the drug, the dosage can be adjusted to achieve a different plasma level using a nomogram devised by Chiba et al.[150] which takes into account the age of the child (Figure 2). The effective therapeutic concentration range of phenytoin is 10 to 20 μg/ml, with toxicity occurring at levels greater than 20 μg/ml.[21,139]

3. Drug Interactions

See Table 5 for a list of drug interactions that have occurred with phenytoin.

4. Toxicity

Nystagmus is associated with blood levels greater than 20 μg/ml, ataxia is associated with levels of 30 to 40 μg/ml, and coma and seizures occur at levels greater than 40 μg/ml.[153] Cardiac toxicity is unlikely following oral overdose; however, rapid intravenous administration may result in dysrhythmias and asystole.[153,154] GI effects include nausea and vomiting. Hyperglycemia has been reported. Hypersensitivity reactions are manifested by skin rashes and fever.[153] Other effects such as dermatitis, hepatitis, gingival hyperplasia, lymphoid hyperplasia, and hemotologic abnormalities are unlikely following acute overdose. A few patients have a hereditary defect in para-hydroxylation and may develop toxicity with therapeutic doses. Fetal hydantion embryopathy syndrome and coagulopathies have been reported in neonates.[154] Treatment of intoxications should focus on symptomatic and supportative care.[47,139,154] Diuresis, hemoperfusion, and hemodialysis are generally ineffective. Exchange transfusion remains controversial.

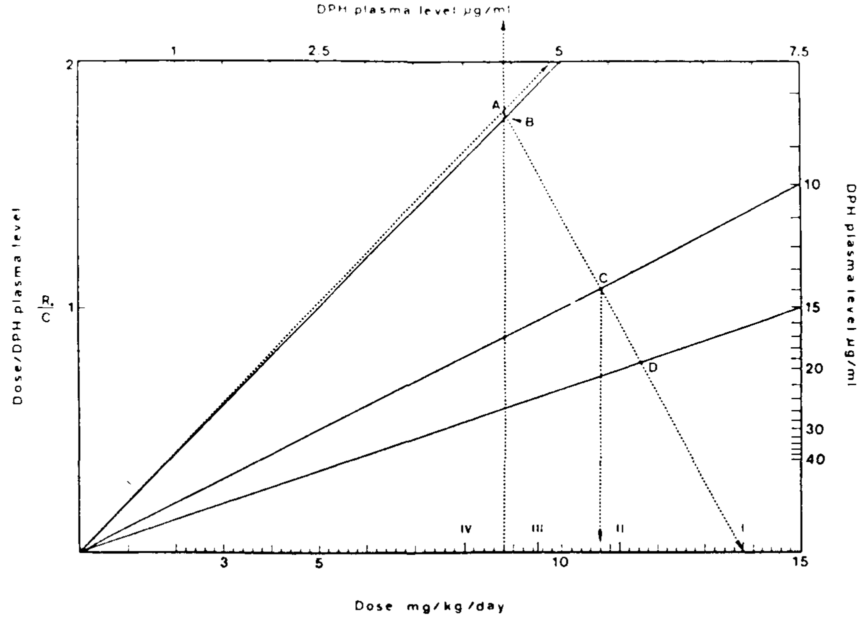

FIGURE 2. Nomogram for adjusting oral phenytoin dosage in children when the daily dose and one serum level are known. As an example, if a 1-year-old child has a level of 4.9 μg/ml on 8.8 mg/kg per dose, a dotted line is drawn vertically from the abscissa (x = 8.8 mg/kg/d) and intersects a dotted line drawn from the origin to the phenytoin level of 4.9 μg/ml. This is point A. Then a line is drawn from point A to the point I on the x axis which indicates the mean value of V_{max} obtained in the age group, i.e., 13.8 mg/kg/d). Three new points are intersected at B, C, and D by this line, with three heavy lines drawn from the origin to the plasma level for maintaining 5, 10, and 15 μg/ml. If we are seeking a final concentration of 10 μg/ml, we draw a vertical line from point C to the bottom of the x axis (i.e., 10.8 mg/kg/d). This dose should yield a phenytoin steady-state concentration of 10 μg/ml. (From Chiba, K., Ishizaki, T., Miura, H., et al., *J. Pediatr.*, 96, 479, 1980. With permission.)

C. TOCAINIDE

A search for an orally available lidocaine analog for the long-term treatment of ventricular dysrrythmias led to the development of tocainide. Tocainide, an amine analog of lidocaine first marketed in November 1984, avoids first-pass hepatic metabolism and is almost 100% bioavailable.[155,156] An oral dose of 600 to 2000 mg/d, given in two or three divided doses, has resulted in a 75% or greater suppression of premature ventricular contractions (PVCs) in 50 to 75% of adult patients.[159,160] However, in patients with sustained ventricular tachycardia induced by programmed ventricular stimulation, tocainide has a fairly low response rate of 10 to 37%.[161,165] In 24 h post-MI, tocainide has resulted in a 75% suppression of PVCs in 56% of patients.[166] Its effect on mortality post-MI has not been evaluated in a large-scale controlled study. It is a reasonably safe and effective antiarrhythmic agent with little hemodynamic effect. Long-term use has a number of side effects.

1. Electrophysiology

Tocainide has electrophysiologic effects similar to lidocaine.[176] At normal potassium levels, the V_{max} is slightly decreased; however, a more depressant effect on the V_{max} is seen at higher potassium levels.[89] Tocainide has no effect on the QRS duration and may cause a slight decrease in the QT duration.

2. Pharmacokinetics and Dosage Recommendations

As mentioned previously, the oral bioavailability of tocainide is very high, approaching 100%. Peak levels are attained in 1 to 1.5 h and the half-life of elimination is 9 to 20 h,[156]

TABLE 5

A. Drugs which Increase Phenytoin Effect

Alcohol
Amiodarone
Anticoagulants
Antidepressants
Chloramphenicol
Cimetidine
Corticosteroids
Disulfiram
Isoniazid
Methsuximide
Miconazole
Nifedipine
Phenylbutazone
Sulfamethoxazole
Sulfonamides
Trazodone
Trimethoprim
Valproic Acid

B. Drugs which Decrease Phenytoin Effect

Antacids
Enteral feedings
Folic acid
Molindone
Pyridoxine
Rifampin
Sucralfate

C. Phenytoin can Decrease the Effectiveness of These Drugs

Benzodiazepine
Carbamazepine
Contraceptives
Corticosteroids
Cyclosporine
Diazoxide
Digoxin
Disopyramide
Estrogen
Furosemide
Haloperidol
Levodopa
Meperidine
Mexiletine
Methadone
Phenothiazine
Quinidine
Tetracycline
Theophylline
Thyroid hormone

Modified from Rizack, M. A. and Hillman, C. D., *The Medical Letter Handbook of Adverse Drug Interactions*, Medical Letter, New Rochelle, NY, 1987. With permission.

and 30.4% of the drug are excreted unchanged in the urine, so appropriate adjustments in dosage should be made in patients with renal or heart failure to allow for reduced clearance rates seen in these states.[124] Renal failure prolongs the $t_{1/2}$ to 27 h and heart failure prolongs the $t_{1/2}$ to 37 h.[156] The therapeutic range for tocainide is 3 to 10 μg/ml with adverse effects occurring at concentrations greater than 10 μg/ml. The oral dose of tocainide in adults is 600 to 2000 mg/d given in two or three divided doses. In a case report of a 2-year-old treated with tocainide, a dose of 150 mg given every 8 h was efficacious in suppressing ventricular dysrhythmias.[167]

3. Drug Interactions

No significant drug interctions have been noted for tocainide. A case report of paranoia induced by concomitant use of tocainide and propranolol has been reported.[168] However, studies of concomitant tocainide and metoprolol administration have not demonstrated any clinically significant interactions.[157]

4. Toxicity

Tocainide is well tolerated hemodynamically. Alterations in left ventricular function are rare for this drug, occurring in only 1.4% of 369 patients receiving it under the compassionate use program.[155] A proarrhythmic effect has been seen in approximately 5% of patients, as assessed by electrophysiologic testing.[169]

The noncardiac side effects of tocainide are primarily neurologic and GI, occurring in about 40% of patients and accounting for 10 to 20% discontinuation of the drug.[156] The GI side effects, which are lessened if the drug is administered with food, include nausea, vomiting, anorexia, and abnormal liver function. Lightheadedness, dizziness, and vertigo have been seen in 12.5% of patients. Parasthesis, tremors, and altered mood were found in 4.6%.[157] Rare but catastrophic side effects include fibrosing alveolitis and interstitial pneumonitis (0.18%), as well as blood dyscrasias including agranulocytosis (0.18%).[156] The hematologic effects of tocainide have greatly limited use of this drug, especially in the U.K.[155,157] Investigators recommend white blood cell counts, especially when initiating therapy. Treatment of tocainide intoxication is similar to that of lidocaine.

D. MEXILETINE

Mexiletine is structurally and electrophysiologically similar to lidocaine with the added advantage of having a high oval bioavailability (90%).[170] It is an effective antiarrhythmic drug with complicated intravenous dosing and a large number of noncardiac side effects that interfere with compliance.

Mexiletine has proven to be effective in the treatment of ventricular dysrhythmias. In a large multicenter clinical trial of patients with benign or potentially lethal ventricular dysrhythmias, 31% of patients treated with mexiletine had at least a 70% reduction of ventricular premature complexes that persisted for 12 weeks, as compared to 32% of those treated with quinidine.[171] Similar results were obtained by Stein and colleagues[172] in a short-term evaluation of 313 patients with ventricular tachyarrhythmias refractory to conventional drugs. Schoenfeld and colleagues[173] achieved complete suppression of inducible ventricular tachycardia in 36% (53 of 148) of patients receiving mexiletine alone or in combination with another antidysrhythmic. In a study of 42 children and young adults treated with mexiletine, 71% of patients exhibited either a 25% reduction in the number of VPBs by 24-h halter or suppression of ventricular tachycardia or couplets induced during treadmill testing.[174] In the latter study, Moak and colleagues[174] found mexiletine to be most effective in patients with congenital heart disease and serious ventricular dysrhythmias.

1. Electrophysiology

Mexiletine decreases the rate of rise of V_{max} by fast sodium channel blockade.[170] Mexiletine causes a decrease in the action potential duration and the relative refractory period in His-Purkinje fibers without affecting the sinus rate, atrioventricular, or His-Purkinje conduction times. AV nodal block is rare and the PR, QRS, and QT intervals are unaffected by mexiletine.[156]

2. Pharmacolokinetics and Dosage Recommendations

Mexiletine is 90% bioavailable and undergoes primarily hepatic elimination with only 10 to 15% of the drug excreted unchanged in the urine.[170] Peak plasma therapeutic concentrations are achieved in 1 to 3 h and the elimination half-life is 9 to 11 h.[156,170] CHF and hemodialysis may prolong mexiletine clearance, while hepatic microsomal enzyme induction may shorten it.[170] Mexiletine exerts little effect on hemodynamics and myocardial contractibility.[124]

Therapeutic plasma levels of mexiletine, i.e., 0.5 to 2.0 μg/ml/l, have been attained in children with dosage ranging from 4.2 to 15 mg/kg/d divided three times.[174] Intravenously a complicated routine of loading dosage is necessary.

3. Drug Interactions

As mentioned previously, hepatic enzyme induction shortens the elimination half-life of mexiletine. Hence, the dosage of mexiletine should be increased with concomitant use of phenobarbital, primadone, rifampin, or phenytoin.[156] Clearance of mexiletine is decreased with concomitant use of cimetidine, isoniazid, chloramphenicol, dicumarol, disulfiram, and methylphenidate.

4. Toxicity

Mexiletine exerts a proarrhythmic effect in 9 to 16% of patients.[173] The principal noncardiac side effects of mexiletine, necessitating discontinuation of the drug in as many as 30% of patients, are GI (nausea) and neurological (lightheadedness, paresthesias, tremors, ataxia, confusion, and loss of memory).[156] The incidence of the noncardiac side effects can be reduced by decreasing the dosage of the drug and/or by administering the drug with food.[173] Treatment of acute intoxication with mexiletine should focus on symptomatic and supportive care.[175]

IV. CLASS IC AGENTS

A. FLECAINIDE

Flecainide was the first of the Class 1C drugs to be approved in the U.S. for treatment of life-threatening ventricular dysrhythmias. In greater than 85% of patients given flecainide, over 80% of premature ventricular contractions has been suppressed.[176,177] In this regard, flecainide is significantly more effective in suppression of PVCs than quinidine (80 vs. 57%) and disopyramide (92 vs. 39%).[177,178] When assessed by programmed electrical stimulation (PES) in patients with more severe ventricular ectopy and/or decreased left ventricular function, flecainide was found to be efficacious in 12 to 65% of patients.[176,179,180] This wide range may reflect different patient populations assessed and different drug dosages employed. Flecainide has also been used for conversion of acute SVT to sinus rhythm and in children for the treatment of SVTs (especially junctional) refractory to conventional drugs.[181-183] It is a potent antiarrhythmic agent, but has numerous cardiovascular effects.

The FDA and the manufacturers, after examining reports on interum data on about 1500 patients assigned to encainide or flecainide, found 56 of 730 died whereas only 22 of 725 given placebo died. This represented greater than a twofold increase in the drug-treated patients. At present, these drugs are indicated only for immediately life-threatening arrhythmias such as sustained tachycardia.

1. Electrophysiology

The electrophysiology feature which distinguishes flecainide and the other Class 1C drugs from the Class 1A and 1B drug is the extremely slow dissociation time of this drug from the sodium channels. This effect causes a marked depression of V_{max} and lengthening of the QRS interval.[184] Flecainide causes a decrease in the APD and ERP in Purkinje fibers, but an increase in the APD and ERP in ventricular fibers, an effect believed to account for the proarrhythmic effect of this drug. Flecainide increases sinus node recovery time and prolongs refractoriness and slows conduction in accessory atrioventricular pathways. In summary, this agent slows depolarization and conduction with little effect on action potential duration. It has a modest negative inotropic effect.

2. Pharmacokinetics and Dosage Recommendation

Flecainide is approximately 95% bioavailable, does not undergo any first-pass hepatic metabolism, and is 10 to 50% excreted unchanged in the urine.[176,184] The elimination half-life in adults is 14 h (range of 7 to 23 h) and in children (ages 3 to 13) ranges from 7 to 10 h.[182] In the latter study, the half-life of elimination of 12 h was attained in a 1 month old. Flecainide is metabolized to two mildly active metabolites, *meta-O*-dealkylated flecainide and its lactam, which are conjugated in plasma.[184] Flecainide clearance is prolonged in patients with CHF and renal failure. The half-life of elimination averages approximately 19 h in CHF and as much as 58 h in end-stage renal failure.[184]

Initial oral dosage of flecainide in adults is 50 to 100 mg BID and may be adjusted every 4 to 5 d, not to exceed 400 mg/d. The therapeutic concentration range for flecainide, not associated with serious side effects, is 0.2 to 1.0 μg/ml.[184] It is not licensed in the U.S. for intravenous use.

3. Drug Interactions

When flecainide and propranolol are administered concomitantly, an increase in plasma levels of 20% for flecainide and 30% for propranolol was noted.[184] Use of digoxin with flecainide may result in a slight increase in digoxin levels.[153] Also, an increase in flecainide toxicity may occur with concomitant administration of amiodarone.

4. Toxicity

A very serious cardiac side effect of flecainide is its proarrythmic effect. Researchers have noted an increase in frequency of sustained ventricular tachycardia (VT) in as many as 20% of patients with a history of sustained VT and impaired left ventricular function.[184] In as many as 300 patients with stable nonsustained VT receiving flecainide, no episode of sustained VT has been reported. The induced dysrhythmias are usually monomorphic, not associated with QRS or QT prolongation, and usually occur at plasma flecainide levels greater than 1.0 μg/ml. The provoked VT may convert to ventricular fibrillation in patients in whom it never did before. Flecainide may also raise the defibrillation threshold, making resuscitatory efforts much more difficult.[176]

Flecainide should be used with caution in patients with decreased left ventricular function since long-term therapy with the drug has resulted in a decrease in the left ventricular ejection fraction.[184] The principal noncardiac side effects of flecainide are CNS disturbances (dizziness and blurred vision) which occur in 10 to 20% of patients and account for discontinuation in 10% of patients.[185]

Cardiac dysrhythmias should be treated with common antidysrhythmic agents, cardioversion, and pacing, depending on the circumstances. The Class 1C agents have been shown to be moderately refractory to standard treatment.[186] Urinary alkalinization should not be used since it decreases flecainide excretion.[50]

B. ENCAINIDE

Encainide is a Class 1C oral agent which is very effective in the treatment of both supraventricular (especially those associated with accessory pathways) and ventricular dysrhythmias. It has little inotropic effect and modest incidence of side effects. In a large multicenter trial (double-blind, placebo-controlled crossover trial) including 187 patients, encainide therapy resulted in a 70% or greater reduction in the frequency of PVCs in 80% of the patients as determined by 24-h halter monitoring.[187] In the same study, 75% of patients exhibited complete elimination of nonsustained VT. Encainide was shown to be more effective and to have less side effects than quinidine in the treatment of ventricular ectopy.[188] As is true for the other available antidysrhythmics, the effectiveness of encainide in preventing dysrhythmias during programmed electrical stimulation is low (23%).[189] See FDA's recommendations for current use under flecainides.

Encainide has proven most efficacious in the pediatric population for the treatment of permanent junctional reciprocating tachycardia (PJRT), arrhythmias responsible for half of the cases of chronic SVT in childhood.[190] PJRT is resistant to all conventional antiarrhythmics. In five of nine patients (mean age of 4 years) with PJRT, encainide alone eliminated 99% of all episodes of PJRT.[191] Encainide has also proven to be effective in the prevention of a rapid ventricular response in patients with WPW syndrome who have atrial fibrillation and an accessory pathway with a short refractory period. It was effective in 53% of patients by PES and in 80% of 50 patients receiving long-term oral encainide therapy for SVT associated with WPW syndrome.[192,193]

1. Electrophysiology

The electrophysiology of encainide is similar to flecainide. Encainide and its metabolites slow intracardiac conduction, are potent Na^+ channel blocking agents, and cause significant QRS widening.[194] Like flecainide, it has a proarrhythmic effect and may depress sinus node function and AV conduction, especially in patients with preexisting pathology.[185] Unlike flecainide, encainide exerts minimal negative inotropic effects.

2. Pharmacokinetics and Dosage Recommendations

Encainide is well absorbed and undergoes extensive hepatic metabolism to the active metabolites, *O*-demethyl encainide (ODE) and 3-methoxy-*O*-demethyl encainide (3-MODE).[156] The half-lives of elimination of encainide, ODE, and 3-MODE are 1.9 ± 0.1, 4 ± 0.5, and 11.4 ± 9.6 h, respectively, and 90% of the population is extensive metabolizers. So, ODE and 3-MODE are primarily responsible for the antidysrhythmic effects. In poor metabolizers, encainide has a longer half-life (5.8 to 13.8 h) and as much as 50% of the drug is eliminated unchanged in the urine.

For adults, the dosage recommendation for encainide is initially 25 mg, three times a day to be increased to 35 mg after 3 to 5 d and then to be increased to 50 mg three times a day after another 3 to 5 d.[194] Dosages greater than 200 mg/d have been associated with increased proarrhythmic effects. In children, the recommended dose, based on body surface, is 60 to 120 $mg/M^2/d$ divided into four doses per day.[190]

3. Drug Interactions

Concomitant use of encainide and cimetidine results in a significant increase (30%) in the levels of encainide and its metabolites ODE and 3-MODE.[195] There are no clinically significant drug interactions between encainide and digoxin, Ca^{2+} channel blockers, diuretics, anticoagulants, oral hypoglycemic agents, antipsychotic agents, and other antidysrhythmic agents.[156]

4. Toxicity

As mentioned previously, encainide like flecainide and other antidysrhythmics exerts a proarrhythmic effect. In a study of 1245 patients, a proarrhythmic effect was noted in 9.2%.[196] In contrast to flecainide, encainide does not exert a negative inotropic effect. The principal noncardiac side effects noted in the study of 1245 patients by Soyka[196] were dizziness (26%), blurred vision (19%), metallic taste (4%), and tremor (3%).

C. PROPAFENONE

Propafenone, an investigational drug, has been classified as a Class 1C drug due to its blockade of fast inward sodium current during phase 0 of the AP, although the drug also possesses some beta-adrenergic blocking activity and calcium channel blocking activity.[197] Propafenone has been used in the treatment of supraventricular and ventricular dysrhythmias, for the control of ventricular rate in patients with WPW syndrome, and specifically in children for postoperative junctional ectopic tachycardia (JET).[35,191,197]

In 60% of patients (34 of 57) treated for ventricular dysrhythmias, propafenone effectively eliminated VT, reduced couplets by 90%, and achieved a 50 to 80% reduction in the frequency of ventricular premature beats.[198] In a double-blind, placebo-controlled study, Hodges et al.[199] noted an 80% or greater reduction in the frequency of PVCs in 58% (7 of 12) of patients receiving propafenone.

Postoperative JET, an often fatal arrhythmia seen in children during the first few days after open heart surgery, has been highly resistant to control with cardioversion, electrical pacing, and drug management.[191] Propafenone treatment, however, has resulted in control of the ventricular rate in six of seven children with postoperative JET.

1. Pharmacokinetics and Dosage

Propafenone is highly bioavailable (95%) and undergoes extensive metabolism.[200] The drug is highly protein bound with an elimination half-life of 5 to 8 h, although a range as broad as 2 to 32 h has been reported. The recommended oral dose of propafenone for adults is 150 to 300 mg two times a day, with antiarrhythmic efficacy occurring in the concentration range of 0.5 to 1.8 μg/ml.[35] The loading dose of propafenone in children for the treatment of postoperative JET is 1.6 to 1.8 mg/kg, administered in 0.2-mg/kg boluses every 10 min until the ventricular rate is brought below 150 per minute, and then a continuous intravenous infusion of 0.004 to 0.007 mg/kg/min is started.[191] The patient can be weaned from the propafenone in 24 to 72 h.

2. Toxicity

Side effects noted with propafenone therapy include AV block, aggravation of ventricular dysrhythmias, congestive heart failure, nausea, weakness, disorientation, and dry mouth.[35] In five of five patients treated with propafenone and digoxin concomitantly, a mean increase of 83% in serum digoxin level was noted.[199]

V. CLASS II AGENTS

A. BETA BLOCKERS

In the pediatric population, beta-adrenergic blocking agents in continuation with digoxin have proved very successful in the treatment of SVT.[201] Beta blockers have also been used for sinus tachycardia associated with thyrotoxicosis and for the treatment of digoxin-induced dysrhythmias, although, in the latter case it is not the drug of choice.[202]

The recommended oral dose of propranolol for the treatment of dysrhythmias is 0.5 to 14 mg/kg/d in four divided doses.[3a] The effective plasma blood level is 20 to 150 ng/ml, although levels as high as 250 ng/ml have been well tolerated.[3a,201] Other pharmacologic details on beta blockers are addressed elsewhere in the book (see Chapter 6).

VI. CLASS III AGENTS

A. AMIODARONE

Amiodarone was approved in December 1985 by the U.S. Food and Drug Administration (FDA) for the treatment of life-threatening ventricular tachydysrhythmias.[203] It is also effective for many supraventricular dysrhythmias, including atrial fibrillation and reentrant tachyarrythmias involving the accessory pathways. The package insert for amiodarone is unusual because it defines the qualifications that physicians should have to prescribe it. It also recommends these that physicians use sophisticated techniques such as electrophysiological studies to assess the efficacy and to monitor the use of the drug. Its approval restricts its use to serious tachydysrhythmias refractory to conventional therapy because it produces numerous side effects, some of which are serious.

1. Electrophysiology

The electrophysiologic profile of amiodarone, a Class III agent, is divergent from previously known antidysrhythmic drugs. It prolongs the duration of the action potential 50 to 90% in all cardiac tissues and decreases phase 4 depolarization.[204] It causes little or no depression of phase 0. Sinus node and junctional automaticity are decreased and PR, QT, and QRS durations are prolonged. Amiodarone also prolongs the effective refractory periods in bypass tracts in patients with the WPW syndrome.

Amiodarone is structurally related to thyroxine. The mechanism of action of amiodarone is that it reduces the outward potassium current as well as the rapid inward sodium current, without being classed as a membrane-stabilizing agent.[205] A single mechanism of action seems to fit poorly with the widespread effectiveness of the drug in a variety of dysrhythmias.

The drug is effective after oral or intravenous administration. It is capable of decreasing peripheral vascular resistance and increasing output and coronary blood flow. Atropine-resistant bradycardia and noncompetitive inhibition of both alpha- and beta-adrenergic receptors are additional pharmacologic effects of amiodarone. Myocardial contractility remains unchanged.

2. Use in Pediatrics

Available information demonstrates that amiodarone may be useful in refractory pediatric ventricular dysrhythmias. Garson et al.[206] treated 39 patients, of whom 13 were under 10 years of age. Among 14 who had VT, the response rate was 79% and there was a low overall incidence of side effects (18%). Coumel and Fidelle[205] treated 135 children under 16 years of age with amiodarone. These authors found that the onset of antidysrhythmic activity of amiodarone was earlier (4.1 d) and there was an earlier return of dysrhythmias after drug withdrawal (3.3 weeks) than customarily seen in adults. They also found the drug to be highly effective and that it had a low incidence of side effects (9%). Keeton et al.[207] reported a study with nearly uniform efficacy, but with a higher incidence of toxicity (58%).

Some have suggested that amiodarone is the drug of choice for WPW syndrome when surgical treatment is not feasible.[206] The drug also appears to be highly successful in controlling most of the supraventricular and ventricular tachydysrhythmias that fail to respond to conventional drugs. Although these are encouraging, the use of amiodarone must be considered experimental because of the relatively brief experience with the drug in infants.

Pregnant and nursing women should not be treated with amiodarone because it is embryotoxic in rats and some strains of mice.[208] There is concern that its high iodine content (75 mg of organic iodine per 200-mg dose) could be released into maternal circulation and ultimately be concentrated in the fetal thyroid gland. Amiodarone crosses the placenta and is excreted into breast milk.[209] Because the drug may remain present in the mother and affect the fetus despite its discontinuation at beginning of pregnancy, it is wise to avoid use of the drug in pregnant women.

3. Pharmacokinetics and Dosage

The GI absorption of amiodarone is poor and variable (bioavailability is 22 to 50%); the onset of action occurs 5 to 10 min after it is given intravenously and 4 to 6 h after oral administration.[204] It is highly protein bound. After cessation of amiodarone therapy, antidysrhythmic action is less than a few weeks in children as opposed to 1 to 2 months in adults.[203] The full effects of the drug necessitate several weeks of use because of the prolonged loading period required to achieve adequate concentrations. There is avid tissue binding. Renal elimination of the drug and its metabolite is negligible. The drug undergoes predominately hepatic metabolism and the mean elimination half-life is 6 to 30 d (25 d after intravenous use and 50 d after chronic oral use) after long-term therapy, although children are believed to metabolize it faster. The recommended dose for infants and children is a loading dose of 10 to 15 mg/kg p.o. or 5 mg/kg i.v., followed 24 h later by a maintenance dose of 5 mg/kg p.o. once daily.[203,207] The intravenous route is not approved in the U.S. Therapeutic blood concentrations are 1.5 to 2.5 μg/ml after several weeks of therapy.

4. Drug Interactions

Amiodarone has been found to interact with numerous drugs. Because of slow elimination, its potential for interaction with another agent persists for months after it is discontinued. Amiodarone has been reported to cause increased concentrations of the following agents: aprindine, digoxin, flecainide, phenytoin, procainamide, quinidine, and warfarin.[203,204] Torsades de pointes, heart block, and atropine-resistant bradycardias have been reported when amiodarone is used in combination with Class 1 antidysrhythmics. Other drugs reported to produce pharmacodynamic interactions with amiodarone are the following: catecholamines, producing alpha- and beta-adrenergic antagonism; diltiazem, producing sinus arrest and hypotension; and propranolol, producing bradycardia and sinus arrest.

5. Adverse Effects and Toxicity

The most severe adverse effect of amiodarone is pulmonary fibrosis, which has a 10% mortality rate. It has occurred in various conditions in 2 to 17% of patients treated with the drug.[210] The onset of this complication may be indistinguishable from congestive heart failure or pneumonia. This effect is usually, but not always, reversible when the drug is stopped. It seems to occur particularly with high doses taken for a long time and in patients with preexisting interstitial lung disease.

Cardiac adverse effects of amiodarone include sinus bradycardia, often severe enough to require a pacemaker, and atrioventricular (AV) block. Amiodarone occasionally has a "proarrhythmic" effect that causes paradoxical worsening of ventricular arrhythmias and has been reported to cause polymorphic VT ("torsade de pointes") with marked QT prolongation. Mild negative effects on contractility do not usually lead to worsening of ventricular function, but congestive heart failure can occur.

Anorexia, nausea, and vomiting are common and occasionally cause weight loss. Asymptomatic abnormalities of liver function tests are also common, but clinical hepatitis and cirrhosis, which can be fatal, have also occurred.[203] CNS reactions include ataxia, dizziness, tremor, difficulty with handwriting, postural instability, decreased ability to concentrate, and mood lability. Peripheral neuropathy and severe proximal myopathy have been reported. Photosensitivity to amiodarone is also common and a bluish gray discoloration of the nose and cheeks, which may not be reversible, develops in 2 to 5% of patients. Virtually all patients develop corneal microdeposits that sometimes cause blurring and other disturbances of vision. The high iodine content of the drug can interfere with thyroid function; both hyper- and hypothyroidism can occur. Conversion of T4 to T3 may be inhibited and both should be measured when evaluating thyroid status.

6. Amiodarone Treatment

Experience with acute overdose is limited and has only been reported in adults. Atropine, beta-adrenergic agonists such as isoproterenol, and temporary pacemaker insertion may be necessary.[211]

B. BRETYLIUM

In the pediatric population, bretylium is the second drug of choice (after lidocaine) for the emergency treatment of ventricular dysrhythmias.[212] There is little experience with the use of this drug in children.[3a]

1. Electrophysiologic Effects

Bretylium is a quaternary ammonium compound that exerts its antidysrhythmic effect both directly on myocardial tissue and indirectly via the adrenergic nervous system.[3a,35] In both ventricular and Purkinje fibers, bretylium prolongs the ERP and ADP simultaneously (without affecting the ratio of these parameters, an action similar to that of amiodarone).

The overall effect of bretylium on the adrenergic nervous system is to cause a surge in the release of norepinephrine from presynaptic terminals which acts on the myocardium and exerts a positive inotropic effect for 30 min. Then it blocks release of norepinephrine and finally blocks reuptake of the neurotransmitter. Bretylium decreases the sinus rate, slows conduction through the AV node, and prolongs the PR and QT intervals without affecting the QRS interval.[3a]

2. Pharmacokinetics and Dosage

Bretylium is poorly and erratically absorbed by the oral route (23%). Although adequately absorbed by the intramuscular route, its onset of action is delayed for at least 1 h compared to the intravenous route. In the emergency setting, the intravenous route is preferred, and 78% of the administered drug is excreted unchanged by the kidneys in 24 h. The average half-life of elimination ranges from 9.8 to 13.6 h. Bretylium has a large volume of distribution (3.3 l/kg) which indicates extensive tissue binding with negligible plasma protein binding. Bennett et al.[213] recommend that patients with a glomerular filtration rate (GFR) of 10 to 50 ml/min receive 25 to 50% of the usual dose given at the normal dosage interval; however, in patients with a GFR of less than 10 ml/min, the drug should be avoided.

In pediatric patients, the recommended dose is 5 mg/kg (500 mg for adolescents and adults) i.v. by rapid infusion followed by another attempt at defibrillation. If ventricular fibrillation persists, the subsequent dose should be 10 mg/kg with countershock repeated. The dose of 5 mg/kg should be given over 8 to 10 min.[214] Patients should be observed for symptoms of severe hypotension. There is little experience with this drug, and it is not recommended at doses greater than 30 mg/kg. It may be given as maintenance by bolus every 6 to 8 h or by infusion at 0.5 to 2 mg/min.

3. Toxicity

The initial release of norepinephrine by bretylium may temporarily increase ventricular ectopic activity and elevate blood pressure. These effects may be enhanced if the patient is receiving vasopressor therapy or if the dysrhythmia being treated is caused by digitalis toxicity. The initial pressor effect is followed by a fall in supine blood pressure (incidence 66%). If the supine systolic pressure falls below 75 mmHg, dopamine or norepinephrine may be infused if necessary.[212]

Other less common adverse effects include nausea, vomiting, bradycardia, anginal attacks, diarrhea, hiccoughs, erythematous macular rash, flushing, fever, sweating, nasal congestion, and mild conjunctivitis.[212] Some patients develop a gray skin discoloration referred to as the ''gray-man syndrome''.

4. Drug Interactions

The following drugs have been reported to decrease bretylium effectiveness: quinidine, guanethidine, and tricyclic antidepressants.[212] Sympathomimetic agents may exert enhanced effects when given with bretylium. It is recommended that bretylium be avoided in digitalis intoxication dysrhythmias.

VII. CLASS IV DRUGS: CALCIUM CHANNEL BLOCKERS

Calcium channel-blocking drugs, also referred to as calcium antagonists or slow channel blockers, have made a major impact on the treatment of disorders such as variant angina, dysrhythmias, and hypertension in adults. The three currently marketed agents in the U.S. are verapamil, diltiazem hydrochloride, and nifedipine. Only verapamil is approved by the FDA for use in children. Among its indications are the treatment of paroxysmal SVT, atrial fibrillation, and atrial flutter.[215] Nifedipine has not demonstrated clinical usefulness as an antidysrhythmic in contrast to verapamil. Nifedipine use in infants is currently experimental.[215] The calcium channel-blocking agents are currently being studied for treatment in a variety of other disorders.[215-217]

A. ELECTROPHYSIOLOGY

This is a chemically diverse group of drugs which shares the common action of inhibiting calcium and sodium influx across the slow channel of cell membranes.[215-223] Since calcium plays a central role in the electrophysiologic and mechanical properties of both cardiac and smooth muscle, these agents affect SA and atrioventricular conduction, myocardial contractility, and vasodilation. Inhibition of the slow calcium channel current will result in:

1. Myocardial depression — negative inotropic response: The order of potency of effect on cardiac muscle is > verapamil > nifedipine > diltiazem.
2. Inhibition of nodal pacemaker tissue — bradycardia: The order of potency of effect on nodal conduction is verapamil > diltiazem. Nifedipine increases AV conduction and shortens refractorines.
3. Inhibition of vasculature tone — peripheral vasodilation: This produces hypotension and coronary vasodilation produces oxygen sparing by decreasing oxygen utilization and increasing oxygen supply. The order of potency of effect on vasculature is nifedipine > diltiazem > verapamil.

Tissue specificity plays a significant role in the use of calcium antagonists. For example, verapamil has a high degree of specificity for nodal tissue and is therefore the drug of choice for the management of supraventricular tachydysrhythmias. In comparison, nifedipine has a high degree of specificity for the vasculature — a property which underlies its efficacy in the management of vasospastic angina. In practice, the choice of which antagonist should be used depends largely on the particular tissue involved.

1. Verapamil

Verapamil directly suppresses sinus pacemaker activity and is one of the most potent inhibitors of AV nodal conduction.[221] A baroreceptor reflex mechanism minimizes sinus slowing of the heart, but mild bradycardia is usually observed. The first sign of verapamil action is prolongation of the PR interval caused by slowing of conduction through the AV node. Verapamil has no effect on the QRS and QT intervals of the electrocardiogram.[222]

Verapamil can also produce a negative inotropic effect on the heart as well as arteriolar vasodilation. Marked vasodilation occurs in peripheral vascular beds, including mesenteric and coronary arteries. Overall, the negative inotropic effects are minimized by the reduction in afterload so that cardiac index is unchanged. Contraindications to the use of verapamil in the young are sick sinus syndrome, severe congestive heart failure, second- or third-degree atrioventricular block, severe hypotension or cardiogenic shock, and concurrent therapy with beta-adrenergic agents.[215] It should not be administered to infants and should be used with caution in children under 6 years.

2. Nifedipine

Very little information is available regarding the use of this agent in children. Nifedipine has been given sublingually for reducing blood pressure in children.[224] This drug has been shown to be useful for treating bronchospasms in children and adults and may also prove useful in management of chronic lung disease in infants.[223] In contrast to verapamil, nifedipine increases AV nodal conduction and shortens AV nodal refractoriness in adults.[216]

3. Diltiazem

No studies are published regarding the use of this agent as an antidysrhythmic in infants

TABLE 6
Therapeutic Pharmacokinetics of Calcium Antagonists

	Nifedipine	Verapamil	Diltiazem
Trade name:	Procardia®	Calan®, Isoptin®	Cardizem®
Dosage			
Child	0.25—0.5 mg/kg (SL)[a]	0.1—0.2 mg/kg i.v. Max 0.3 mg/kg	Not available
Absorption			
Oral (%)	>90	>90	>90
Bioavailability (%)	65—70	20—30	<20
Onset of action			
Sublingual (min)	3	—	—
Oral (min)	<20	<30	<30
Intravenous (min)	<1	<2	—
Peak effect	1—2 h (oral)	5 h (i.v., 5—15 min)	30 min
Therapeutic plasma concentration (ng/ml)	25—100	15—100	30—130
Protein binding (%)	90	90	80
Plasma half-time			
Initial fast (A) (min)	150—180	15—30	20
Slow (B) (h)	5	3—7	4
Metabolism	Extensively metabolized to an inert free acid and lactone	Extensive first-pass hepatic extraction, metabolized to norverapamil	Extensively deacetylated
Excretion			
Renal (%) (mostly metabolites)	70 first day (80 total)	50 first day (70 total)	35 (total)
Fecal (%)	<15	15	65

[a] SL, sublingual.

Modified from Henry, P. D., *Am. J. Cardiol.*, 46, 1047, 1980. With permission.

or children. In adults, diltiazem produces slowing of the AV nodal conduction equivalent to that of verapamil, but produces less prolongation of AV refractoriness.[222]

B. PHARMACOKINETICS

Table 6 demonstrates a wide variation in pharmacokinetics between the calcium channel blockers. Generally, these agents are well absorbed, but verapamil has a large first-pass extraction (70% of the therapeutic dose). Calcium channel blockers are highly protein bound and lipophilic and exhibit a large apparent volume of distribution (>2 l/kg). Elimination occurs almost exclusively by the liver. Oxidation of verapamil to norverapamil is the primary metbolite which has mild hemodynamic effects in dogs.[216] Nifedipine metabolites are inactive despite primarily hepatic elimination. The action of nifedipine is enhanced during severe renal failure.[225a] Both verapamil[225b,226] and diltiazem[227] diffuse into breast milk with reported levels in neonates of about 5 to 10% of the mother's level.

C. DOSAGE

1. Verapamil

The recommended initial dose of verapamil is 0.075 to 0.15 mg/kg i.v. (adolescent and adult dose is 5 mg) over 1 to 2 min under ECG and blood pressure monitoring. The maximum cumulative dose should be no greater than 0.3 mg/kg.[221] Oral dose is 2.5 to 7 μg/kg/d. The peak is reached in 5 to 15 min intravenously. No information is available on maintenance therapy in infants or children. The safety and value of verapamil in infants less than 6 months old are very controversial. Long-term infusion in adults is 0.06 to 1.3 mg/kg/h. Because liver disease causes a decrease in metabolism of verapamil, dosage adjustments are often necessary.[215] Avoid use in wide QRS complex regular tachycardia of unknown origin.

2. Nifedipine

In children, doses of 0.25 to 0.5 mg/kg given sublingually have been successful in reducing blood pressure without significant complications.[224] No dosing information is available for infants.

3. Diltiazem

No dosing information is available for infants or children.

D. DRUG INTERACTIONS

1. Verapamil

Drug interactions between verapamil and digoxin or propranolol have been reported.[228-232] An increase of digoxin levels by 77% after 2 weeks of verapamil use has occurred. The concurrent use of propranolol and verapamil may increase the risk of hypotension, bradycardia, and asystole.[230] Class IA agents should be used with extreme caution because of the potential for hypotension and bradycardia. Disopyramide should not be administered within either 48 h before or 24 h after intravenous verapamil.[231] Intravenous verapamil should not be mixed with alkaline solutions because a precipitate will form.

2. Nifedipine

Drug interactions between nifedipine and digoxin or beta blockers have been reported, but these drugs may be administered with extreme caution and proper monitoring.[231]

3. Diltiazem

Caution is advised when using this drug with digoxin and beta-blockers.

Agents that decrease hepatic blood flow such as cimetidine can be expected to increase the half-life of the calcium antagonists. Caution should be used with agents that are normally degraded by hepatic microsomal oxidases such as anticoagulants, sulfonylureas, and anticonvulsants.[231]

E. TOXICITY

Cardiovascular complications of calcium channel blockers can be explained by their action on peripheral vasculature, cardiac inotropy, and conduction. Vasodilation may give rise to hypotension and reflex tachycardia and contribute to the development of edema of the lower extremities. The negative inotropic effect of verapamil may worsen heart failure in patients with compromised cardiac function.[232] Hypotension and bradycardia have occurred in infants who were treated with verapamil for SVT.[233] The incidence of side effects of verapamil in adult patients is approximately 10%, with 1% of the patients requiring discontinuation of the drug. Patients being treated concurrently with beta-blocking drugs are at special risk because of the additional negative chronotropic effect of those agents.[230]

Adverse effects on the CNS may result from several mechanisms. Headache is commonly associated with nifedipine therapy and is probably due to vasodilation. Vertigo and dizziness are less common, but may reflect decreases in systemic blood pressure.[230] In addition, cerebral ischemia, hemiparesis, aphasia, and sudden loss of consciousness have been reported from nifedipine.[234,235] GI tract symptoms including nausea, vomiting, constipation, and hepatitis have been reported from calcium channel blockers.

In acute overdoses, hypotension and bradycardia are reported frequently 1 to 5 h post-ingestion,[232,236] and 10 mg of sublingual nifedipine has been reported to cause hypotension, myocardial ischemia, and infarction in a matter of minutes.[237] AV dissociation, sinus arrest, and asystole have occurred following intravenous verapamil.[238] Ingestion of 400 mg of verapamil in an 11 month old resulted in seizures in 45 min.[236] Nifedipine increases the heart rate, and cardiogenic shock and idioventricular rhythm have been reported in patients with underlying cardiovascular diseases.[239] A 74-year-old man who ingested 1500 mg of diltiazem developed bradycardia diaphoresis, mental confusion, and slurred speech.[234]

The specific antagonist for the toxic manifestations of overdose with calcium channel blockers is calcium. Controversy exists regarding which calcium preparation to use. Some authors caution against the use of calcium chloride because of its potential vasodilating effect and suggest that the gluconate form be used.[241] Others suggest that the chloride preparation is more effective because of its predictable increase in extracellular ionized calcium.[242]

Calcium chloride (10%, 27.9 mg or 1.36 meq of calcium per milliliter) should be given under ECG monitoring to any patient not responding to supportive therapy alone. Calcium is given intravenously in doses of 10 to 20 mg/kg per dose (0.10 to 0.20 ml/kg per dose) in pediatric patients and up to 1 g (10 ml per dose) in adults.[243]

As an alternative, calcium gluconate (10%, 9 mg or 0.45 meq of calcium per milliliter) can be used. It can be given intravenously in doses of 2.7 mg/kg per dose (0.3 ml/kg per dose) in pediatric patients and up to 1 g (10 ml per dose) in adults over 5 to 10 min.

Dopamine can be used if necessary (2 to 10 μg/kg/min i.v. infusion). Doses above 10 μg/kg/min may cause systemic and renal vasoconstriction. Symptomatic bradycardia, heart block, and asystole have not responded consistently to calcium and atropine. The dose of atropine in children is 0.01 to 0.03 mg/kg (minimum of 0.15 mg) and in adults it is 0.5 to 1.0 mg. Isoproterenol can be used if necessary; a pacemaker may be needed as well. Severe rapid VT in patients with WPW syndrome needs cardioversion.[244] Calcium will often restore the blood pressure, but has little effect on the antidysrhythmic activity of veraprami1.

VIII. DIGOXIN

Digoxin, a cardiac glycoside, is widely used as a positive inotropic agent in the treatment of congestive heart failure and in controlling rapid ventricular response to atrial fibrillation and flutter.

A. ELECTROPHYSIOLOGY

Digoxin exerts its positive inotropic effect by altering excitation-contraction coupling and increasing the intracellular calcium concentration of myocardial fibers, thereby making more calcium available to bind with troponin during muscle contraction. This leads to increased strength of contraction and, hence, the positive inotropic effect.

Digoxin binds with high affinity to cell membrane-bound sodium-potassium ATPase and blocks the sodium-potassium pump partially. This pump inhibition causes an increase in the intracellular sodium concentration, normally kept very low by the pump, which becomes available for exchange with extracellular calcium. The sodium-calcium exchange is believed to occur by a cell membrane exchange mechanism, with the influx of calcium increasing due to the increased intracellular sodium available for exchange.[245]

Digoxin exerts both direct and indirect effects on the cardiac conduction system. It directly affects the Purkinje fibers by increasing the slope of phase 4 depolarization and by causing the appearance of delayed after depolarizations, both of which may be responsible for the ectopic activity seen in digoxin toxicity. Digoxin also directly (1) causes a decreased action potential duration in atrial and ventricular muscle fibers, (2) increases the slope of phase 2, and (3) decreases the slope of phase 3 in these fibers.[246] These effects are apparently responsible for the digoxin effects seen on ECG which are a decreased QT duration and

TABLE 7
Dosage Guidelines for Digitalis Glycosides

	Digoxin	**Digitoxin**
Dosage range Child	Initial loading dose (oral) Premature: 20—30 μg/kg Full term: 25—35 μg/kg 1—24 months: 35—60 μg/kg 2—5 years: 30—40 μg/kg 5—10 years: 20—35 μg/kg >10 years: 10—15 μg/kg Loading dose (i.v.) 80% of p.o. TDD $^1/_2$ TDD first, then $^1/_4$ TDD q 6—8 h for two doses Maintenance dose (oral/i.v.) Premature: 20—30% p.o. TDD All others: 25—35% p.o. TDD	Loading dose (oral/i.v.) 25—35 μg/kg over 12—24 h Maintenance dose 10—25% total loading dose daily
Adult	Loading dose (i.v.) 8—10 μg/kg For CHF: 13—15 μg/kg for atrial fibrillation over 12—24 h Maintenance dose 0.125—0.5 mg/d	Loading dose (p.o./i.v.) 0.8—1.4 mg over 12—24 h or 10—15 μg/kg Maintenance dose 10% of total loading dose

Note: TDD, total daily dose.

ST/T changes. The SA and AV nodes are not significantly affected at therapeutic digoxin levels, but are directly suppressed at toxic levels.

The indirect effects of digoxin appear to be secondary to increased systemic perfusion with a resultant reflex decrease of sympathetic tone and increase of vagal tone on the heart.[246] Digoxin is also believed to have a direct effect on the vagal nuclei in the brain stem, further potentiating an increase in cardiac vagal tone. It may also sensitize peripheral baroreceptors, increasing their afferent tone to the vasomotor center and causing yet more increased cardiac vagal tone. These indirect effects cause decreased SA and AV node activity and increase the effective refractory period in the AV node. This is believed to be the mechanism by which digoxin slows the ventricular response to atrial flutter and fibrillation.

B. PHARMACOKINETICS AND DOSING RECOMMENDATIONS

Digoxin is available as 0.125-, 0.25-, and 0.5-mg tablets, a 0.05-mg/ml elixir, and an injectable form with 0.25 mg/ml. Bioavailability ranges from 50 to 80% and is dependent on tablet dissolution.[247] After oral administration, the peak effect is noted in 3 to 6 h.[246,247] Digoxin is about 25% bound to plasma proteins and has a large volume of distribution, 5 to 7 l/kg in adults, which makes hemodialysis ineffective as a treatment for acute and chronic digoxin toxicity.[246,248] The route of elimination is primarily by the kidneys which excrete 60 to 80% of digoxin unchanged. The elimination half-life is 1.5 to 1.7 d.[246,249]

If the digitalis effect is needed rapidly, then a large loading dose is required due to the relatively long elimination half-life. This is called the digitalization dose and is the approximate amount which provides a steady-state total body store large enough to give the desired therapeutic effect.[246] This digitalizing dose can be given intravenously when the digoxin effect is needed urgently, in which case the peak effect is seen in 5 to 30 min. After the loading dose, a daily maintenance dose of approximately 35% of total body stores is given to equal the daily loss. The therapeutic plasma concentration is 0.5 to 2.0 ng/ml, but it may be higher in infants (up to 4.0 ng/ml). Table 7 gives the recommended loading and maintenance doses.[248]

TABLE 8

Increased digoxin effect	Decreased digoxin effect
Amiodarone	Aminoglycosides
Amphotericin B	Antacids
Anticholinergics	Cholestyramine
Benzodiazepines	Corticosteroids
Cimetidine	Hydralazine
Diltiazem	Kaolin-pectin
Erythromycins	Metoclopramide
Ethacrynic acid	Nitroprusside
Flecainide	Penicillamine
Furosemide	Phenytoin
Hydroxychloroquine	Procarbazine
Hypoglycemics	
Nonsteroidal antiinflammatory drugs	
Propafenone	

Modified from Rizack, M. A. and Hillman, C. D., *The Medical Letter Handbook of Adverse Drug Interactions*, Medical Letter, New Rochelle, NY, 1987. With permission.

Pediatric patients require higher dosages, both loading and maintenance, than adults. This has been justified because of the more rapid elimination of digoxin and a larger volume of distribution in pediatric patients.[256] The volume of distribution is 7.5 l/kg for neonates and 16 l/kg for infants and children.

An important factor in evaluating the digoxin plasma levels in neonates, infants, and children is the presence of an endogenous digoxin-like substance which cross-reacts with most immunoassay antibodies for digoxin.[255] Apparent digoxin concentrations have been measured in pediatric patients, especially those under 6 months of age who were not on cardiac glycoside therapy; levels as high as 4.1 ng/ml have been measured in neonates.

C. DRUG INTERACTIONS

In patients with WPW syndrome who have episodes of atrial flutter or fibrillation, digoxin has the potential to decrease the effective refractory period of the anomalous bypass tract and to allow a rapid ventricular response which may degenerate into ventricular fibrillation.[245,246] Coadministration of quinidine results in an increased digoxin plasma concentration because quinidine displaces digoxin from tissue binding sites, decreases renal clearance, and decreases the apparent volume of distribution of digoxin. The average change in plasma concentration is a twofold increase in a few days.[246,247]

Calcium channel blockers, amiodarone, and spironolactone also increase digoxin levels, at least in part due to a decrease in renal clearance of digoxin.[247] Table 8 lists agents that interact with digoxin.

D. ECG MANIFESTATIONS

Digoxin therapy causes characteristic effects on the ECG which can be anticipated in most patients as they approach adequate blood levels, but these ECG changes are not useful in estimating digoxin dosage or degree of digitalization. This digoxin effect does not indicate toxicity. It is first manifested by S-T segment depression with upward concavity, giving a scooped-out appearance, and/or T-wave flattening or inversion. The QT interval is shortened and the PR interval is slightly prolonged.[246,250] Digoxin does not cause QRS widening.

Digoxin toxicity, although not a pure electrocardiographic diagnosis, can mimic heart disease and has prominent effects on the ECG. No arrhythmia is diagnostic for digoxin toxicity. The toxic effects seen on ECG are due to either suppressant effects, excitant effects, or a combination of both. The suppressant effects may be due to both the indirect vagal effect and a direct toxic effect on the SA and AV nodes and Purkinje fibers. Sinus bradycardia and all forms of SA and AV block can occur.[250] The excitant effects may be due to the increased phase 4 slope, delayed after depolarizations, and decreased effective refractory period, allowing reentry, and include ventricular ectopy — especially bigeminy, atrial tachycardia, AV junctional tachycardia, and ventricular tachycardia or fibrillation.[247,250,251] Combined effects can result in numerous arrhythmias including atrial tachycardia with varying AV block.

E. TOXICITY

Digoxin has a low therapeutic index. While blood levels correlate roughly with toxicity, there is considerable overlap between therapeutic and toxic levels.[252] Digoxin toxicity can exhibit a myriad of manifestations. The diagnosis is clinical, and no sign, symptom, or ECG manifestation is diagnostic. The GI system is frequently affected in both acute and chronic toxicity. Anorexia, nausea, vomiting, and diarrhea can occur. CNS and visual disturbances also occur in both acute and chronic toxicity. Headache, fatigue, confusion, delirium, and hallucinations can occur as well as disturbances in color or pattern vision and blurring.[247] Cardiac rhythm disturbances are the most common and dangerous manifestations of digoxin toxicity[251] and these have been previously described. Hypokalemia and hypomagnesemia can exacerbate these dysrhythmias as can hypercalcemia.

Acute intoxication is often associated with hyperkalemia, bradyarrhythmias, and AV nodal conduction disturbances. Chronic toxicity is often associated with normo- or hypokalemia, along with atrial or nodal tachycardia and ventricular dysrhythmias.[246,247] Acute intoxication in pediatric patients appears to be fairly well tolerated and is not often associated with hyperkalemia or life-threatening arrhythmias.[253] In acute overdose, levels up to 10 ng/ml can be tolerated without serious toxicity by children who do not have preexisting cardiovascular disease.[247] Due to the short alpha-phase half-life of digoxin, along with the complete distribution time of 5 to 6 h, serum concentrations determined less than 6 h postingestion may be high and give a false impression of severity.[253]

Treatment of the acute overdose includes GI decontamination with lavage and activated charcoal. Emesis is not recommended because of possible increased cardiac vagal effect. Hemoperfusion or hemodialysis are not useful due to the large volume of distribution of digoxin. Hyperkalemia should be treated, if severe, but calcium should not be given. Atropine is effective for bradyarrhythmias. Ventricular arrhythmias can be treated with lidocaine or phenytoin. However, cardioversion should be avoided.

In life-threatening situations, Digibind®, a digoxin-specific antibody, fragment can be given. It acts within 30 to 60 min and has a complete response within 3 h. The serum digoxin level rises dramatically, but free digoxin falls and the digoxin-antibody fragment complex is eliminated by the kidneys. Avoid countershock in digitalis intoxication. It is also recommended that calcium channel blockers not be used.

IX. ABBREVIATIONS

APD	Action potential duration
ERP	Effective refractory period
SA	Sinoatrial
AV	Atrioventricular node
SVT	Supraventricular tachycardia
WPW	Wolff-Parkinson-White syndrome

V_{max}	Maximum rate of rise of phase 0 during depolarization
NAPA	*N*-Acetyl procainamide
PVC	Premature ventricular contraction

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Chapter 6

DIAGNOSIS AND MANAGEMENT OF HYPERTENSION IN PEDIATRICS

Albert P. Rocchini

TABLE OF CONTENTS

I. Introduction 118

II. Essential Hypertension 118

III. Diagnostic Evaluation of the Hypertensive Child 123
  A. History 123
  B. Physical Examination 124
  C. Laboratory Tests 124
    1. Urinalysis 124
    2. Blood Chemistries 124
    3. Echocardiogram 124
    4. Intravenous Pyelogram, Renal Ultrasound, and Renal Scan 125
    5. Peripheral Plasma Renin Activity 125

IV. Categorization of Children with Hypertension 125

V. Management of Systemic Hypertension 126
  A. Hypertensive Crisis 126
  B. Chronic Hypertension 127
    1. Nonpharmacologic Management 127
    2. Pharmacologic Management 128

VI. Antihypertensive Medications 128
  A. Diuretics 128
    1. Benzothiadizianes 128
    2. Loop Diuretics 129
    3. Potassium-Sparing Diuretics 132
  B. Adrenergic Inhibitors 132
  C. Direct Vasodilators 134
  D. Angiotensin-Converting Enzyme Inhibitors 134
  E. Calcium Channel Blockers 135
  F. Aims of Treatment 136

References 136

I. INTRODUCTION

During the past 20 years, it has become increasingly clear that hypertension constitutes a major disease process in children as well as adults. Prior to 1977, most of the data concerning the prevalence of hypertension and the mechanisms involved in the development of hypertension have centered on the adult population. However, starting in 1977 with the publication of the first "Report of the Task Force on Blood Pressure Control in Children,"[1] there has been a surge of interest in systemic hypertension in children and adolescents.

The incidence of hypertension in the pediatric age group is reported to vary from 0.6 to 11%. The variability in prevalence rates is directly related to the age group investigated and the criteria used to define hypertension.[2-8] Unlike the adult population, there is no single blood pressure level that can be used to diagnose hypertension in the child. Recent studies have reported the relationship between blood pressure and various anthropometric indices, such as height, weight, body surface area, and various ratios derived from these values.[9,10] Although we do not have a universally accepted standard of the normal distribution of blood pressure from birth to maturity, based on data from nine large, reasonably well-conducted studies, the second report of the Task Force on Blood Pressure Control in Children has described age-specific distributions of systolic and diastolic blood pressure for boys and girls (ages 0 to 18 years) (Figure 1).[11] Despite the fact that the task force grids have been updated, they still suffer from a number of shortcomings:[7,12-15] (1) the blood pressures were not obtained in a standardized fashion and (2) the blood pressure grids do not take into account the effects of differences in body size (height and weight) and pubertal stage.

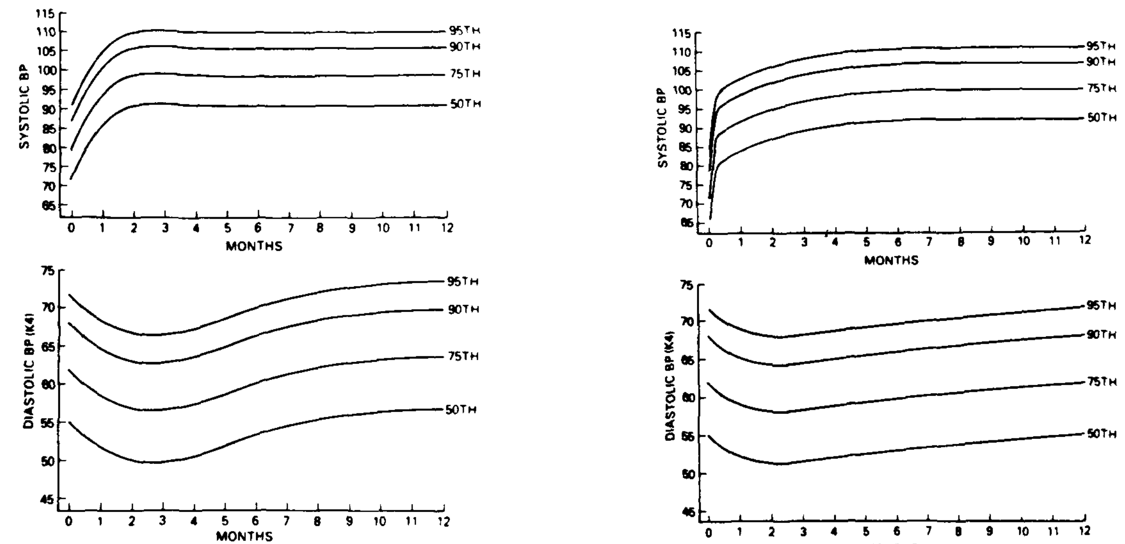
In conjunction with the new blood pressure distributions that have been outlined by the Second Task Force report,[11] we currently define an elevated blood pressure level in any child as a blood pressure that is at least above the 90th percentile for age and sex. The blood pressure should be measured in the sitting position with a cuff of appropriate width (covering two thirds of the upper arm) and at least three readings should be taken with only the last two being averaged for the recorded blood pressure. Although the findings of an elevated blood pressure on physical examination constitutes an abnormal sign, it does not mean that hypertension (i.e., sustained blood pressure elevation) is present. Therefore it has been recommended that for a child to be diagnosed as having hypertension it is required that the blood pressure elevation be abnormal (at least above the 95th percentile rank for age and sex) on at least three separate examinations over a 6- to 12-month interval if not associated at the time of the initial examination with signs and/or symptoms commonly found with hypertensive cardiovascular disease (i.e., evidence of cardiac hypertrophy either by electrocardiogram [ECG] or echocardiogram), symptomatic hypertensive encephalopathy (headache, dizziness, or seizures), or hypertensive retinopathy). Table 1 presents an age group classification of severe hypertension, as defined by the Second Task Force.[11]

Once it has been determined that the child has hypertension, the etiology of the hypertension needs to be established in order to provide appropriate therapy. We prefer to divided hypertension into two major categories: essential (or primary) and secondary.

II. ESSENTIAL HYPERTENSION

The majority of adults with hypertension are classified as having essential hypertension (i.e., without any identifiable cause). However, in childhood there is considerable controversy as to the prevalence and natural history of essential hypertension. The reported incidence of essential hypertension in the pediatric population ranges from 5 to 80%.[7,16-18]

Data from three referral centers in the U.S., Canada, and the U.K.[16-18] indicate that the vast majority of children investigated for significant hypertension are found to have renal disease. However, it should be emphasized that the data in these three studies are based on



90TH PERCENTILE

SYSTOLIC BP	87	101	106	106	106	105	105	105	105	105	105	105	105
DIASTOLIC BP	68	65	63	63	63	65	66	67	68	68	69	69	69
HEIGHT CM	51	59	63	66	68	70	72	73	74	76	77	78	80
WEIGHT KG	4	4	5	5	6	7	8	9	9	10	10	11	11

BOYS 0-12 mon

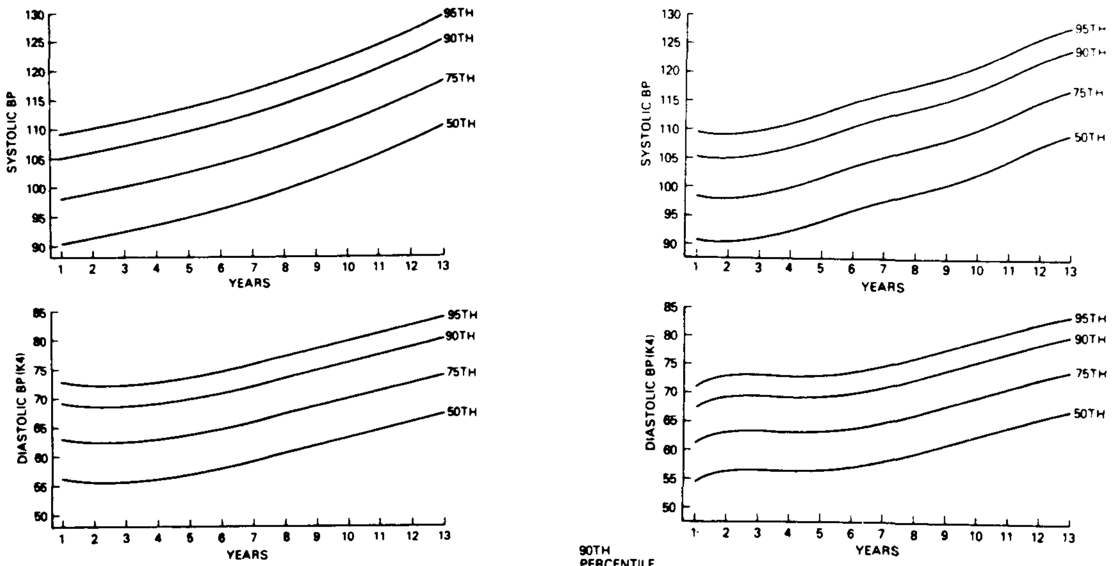
90TH PERCENTILE

SYSTOLIC BP	76	98	101	104	105	106	106	106	106	106	106	105	105
DIASTOLIC BP	68	65	64	64	65	65	66	66	66	67	67	67	67
HEIGHT CM	54	55	56	58	61	63	66	68	70	72	74	75	77
WEIGHT KG	4	4	4	5	5	6	7	8	9	9	10	10	11

GIRLS 0-12mon

A

FIGURE 1. Age-specific percentiles of blood pressure measurements in boys and girls. (A) Birth to 12 months of age (Korotkoff phase IV used for diastolic blood pressure); (B) 1 to 13 years of age (Korotkoff phase IV used for diastolic blood pressure); (C) 13 to 18 years of age (Korotkoff phase V used for diastolic blood pressure). (From Report of the Second Task Force on Blood Pressure Control in Children — 1987, *Pediatrics*, 79, 1, 1987. With permission.)



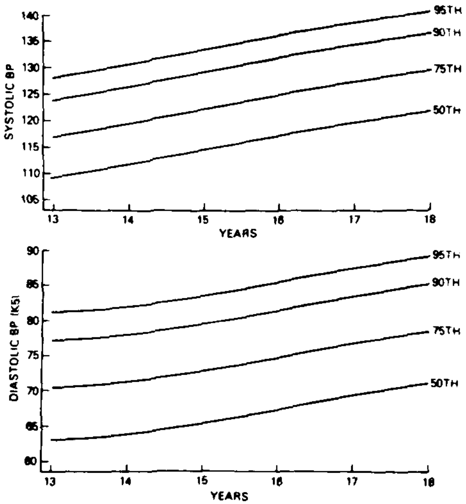
90TH PERCENTILE													
SYSTOLIC BP	105	106	107	108	109	111	112	114	115	117	119	121	124
DIASTOLIC BP	69	68	68	69	69	70	71	73	74	75	76	77	79
HEIGHT CM	80	91	100	108	115	122	129	135	141	147	153	159	165
WEIGHT KG	11	14	16	18	22	25	29	34	39	44	50	55	62

BOYS 1–13yr

90TH PERCENTILE													
SYSTOLIC BP	105	105	106	107	109	111	112	114	115	117	119	122	124
DIASTOLIC BP	67	69	69	69	69	70	71	72	74	75	77	78	80
HEIGHT CM	77	89	98	107	115	122	129	135	142	148	154	160	165
WEIGHT KG	11	13	15	18	22	25	30	35	40	45	51	56	63

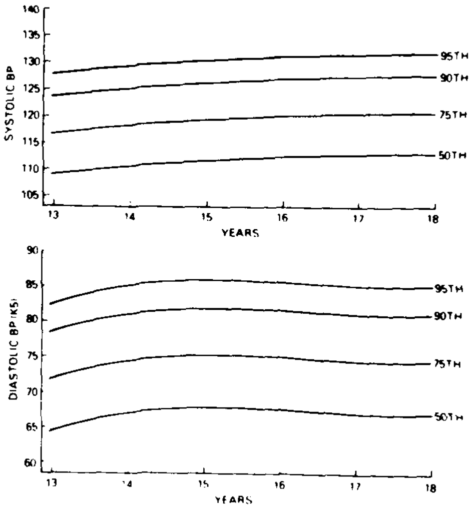
GIRLS 1– 13yr

FIGURE 1B.



90TH PERCENTILE						
SYSTOLIC BP	124	126	129	131	134	136
DIASTOLIC BP	77	78	79	81	83	84
HEIGHT CM	165	172	178	182	184	184
WEIGHT KG	62	68	74	80	84	86

BOYS 13–18yr



90TH PERCENTILE						
SYSTOLIC BP	124	125	126	127	127	127
DIASTOLIC BP	78	81	82	81	80	80
HEIGHT CM	165	168	169	170	170	170
WEIGHT KG	63	67	70	72	73	74

GIRLS 13– 18yr

FIGURE 1C.

TABLE 1
Classification of Hypertension by Age Group

Age group	Significant hypertension (mmHg)	Severe hypertension (mmHg)
Newborn	Systolic BP ≥ 96	Systolic BP ≥ 106
7 d	Systolic BP ≥ 104	Systolic BP ≥ 110
8—30 d		
Infant (<2 years)	Systolic BP ≥ 112	Systolic BP ≥ 118
	Diastolic BP ≥ 74	Diastolic BP ≥ 82
Children (3—5 years)	Systolic BP ≥ 116	Systolic BP ≥ 124
	Diastolic BP ≥ 76	Diastolic BP ≥ 84
Children (6—9 years)	Systolic BP ≥ 122	Systolic BP ≥ 130
	Diastolic BP ≥ 78	Diastolic BP ≥ 86
Children (10—12 years)	Systolic BP ≥ 126	Systolic BP ≥ 134
	Diastolic BP ≥ 82	Diastolic BP ≥ 90
Adolescents (13—15 years)	Systolic BP ≥ 136	Systolic BP ≥ 144
	Diastolic BP ≥ 86	Diastolic BP ≥ 92
Adolescents (16—18 years)	Systolic BP ≥ 142	Systolic BP ≥ 150
	Diastolic BP ≥ 92	Diastolic BP ≥ 98

From Report of the Second Task Force on Blood Pressure Control in Children — 1987, *Pediatrics*, 79, 1, 1987. With permission.

a series of patients hospitalized in major referral centers. Since establishing a preventive cardiology clinic at the University of Michigan in 1981, we have had over 250 children referred by primary care physicians for evaluation of possible hypertension. Of these children, about 25% did not meet our definition of hypertension (i.e., persistent blood pressures greater than the 95th percentile for age and sex on at least three separate examinations over 6 to 12 months). The causes of persistent hypertension in the remaining children included:

1. Essential hypertension was present in 55% (76% of these children were obese).
2. Renal disease was present in 30% (11% of these children have renovascular disease).
3. Coarctation of the aorta was present in 8%.
4. Endocrine disorders were present in 6%.
5. Miscellaneous disorders were present in 1%.

Thus, in our group of patients, unlike the other three large studies, essential hypertension accounted for 55% of our cases. However, it is important to note that a patient with an obvious cause for their hypertension, such as glomerulonephritis, is not usually referred to our preventive cardiology clinic. There are other studies that also confirm that essential hypertension is the most common cause of hypertension in the pediatric age group. Ogborn and Crocker[19] reported that of 103 children referred to the Izaak Walton Killam Hospital for Children for the evaluation of hypertension, 56% had essential hypertension. Rames et al.[7] presented data on 44 cases of hypertension acquired from 6672 school children surveyed in Muscatine, IA. All 44 cases met the criteria outlined above for sustained elevation of blood pressure. Of these 44 children, 5 (12%) had secondary hypertension and the remaining 39 children had essential hypertension (23 or 56% were obese). Thus, it appears that for the general pediatric population, the incidence of essential hypertension may not be much different from that reported to occur in the adult population.

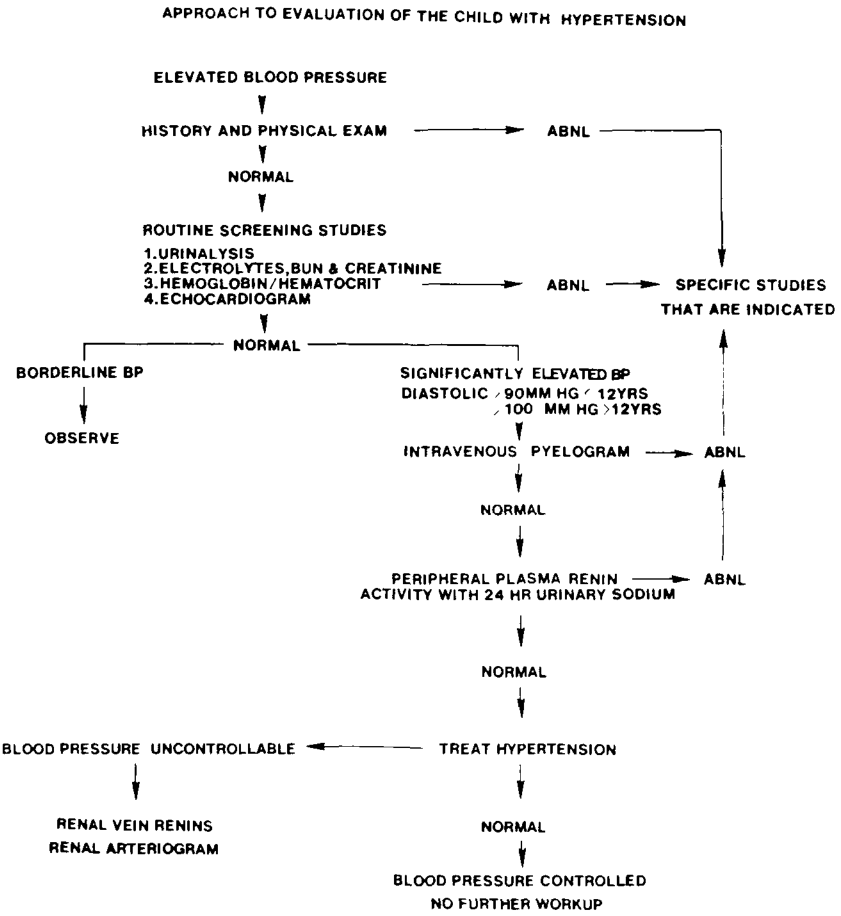

APPROACH TO EVALUATION OF THE CHILD WITH HYPERTENSION
ELEVATED BLOOD PRESSURE
HISTORY AND PHYSICAL EXAM
ABNL
NORMAL
ROUTINE SCREENING STUDIES
1.URINALYSIS
2.ELECTROLYTES,BUN & CREATININE
3.HEMOGLOBIN/HEMATOCRIT
4.ECHOCARDIOGRAM
ABNL
SPECIFIC STUDIES THAT ARE INDICATED
NORMAL
BORDERLINE BP
OBSERVE
SIGNIFICANTLY ELEVATED BP
DIASTOLIC >90MM HG <12YRS
>100 MM HG >12YRS
INTRAVENOUS PYELOGRAM
ABNL
NORMAL
PERIPHERAL PLASMA RENIN ACTIVITY WITH 24 HR URINARY SODIUM
ABNL
NORMAL
BLOOD PRESSURE UNCONTROLLABLE
TREAT HYPERTENSION
RENAL VEIN RENINS
RENAL ARTERIOGRAM
NORMAL
BLOOD PRESSURE CONTROLLED
NO FURTHER WORKUP

FIGURE 2. A diagnostic approach to the evaluation of the child with a sustained elevation in blood pressure (abbreviations: abnl, abnormal; BUN, blood urea nitrogen). (From Rocchini, A. P., *Pediatr. Clin. North Am.*, 31, 1259, 1984. With permission.)

III. DIAGNOSTIC EVALUATION OF THE HYPERTENSIVE CHILD

All children who have blood pressures above the 95th percentile on three or more occasions measured over a 6- to 12-month period should be evaluated. An approach to the evaluation of the child with sustained elevation in blood pressure is outlined in Figure 2.

A. HISTORY

The cornerstone in the diagnostic evaluation of childhood hypertension is a careful medical history. The areas that should be pursued are

1. Symptoms associated with specific diseases, such as unexplained fevers in pyelonephritis; leg pains with exercise in coarctation of the aorta; polyuria, weakness, and muscle cramps in hyperaldosteronism; weight loss, fine tremor, and sweating in hyperthyroidism; and sweating and palpitation in pheochromocytoma
2. Medications or chemicals that can elevate blood pressure (such as birth control pills, steroids, amphetamines, sympathomimetic agents, heavy metal, etc.)
3. A history of trauma

4. A family history of hypertension
5. A past history, such as placement of an umbilical artery catheter, recurrent urinary tract infection, and others

B. PHYSICAL EXAMINATION

The physical examination should be directed to detect findings suggestive of definable causes of hypertension and to uncover any target organ damage. Serial measurements of height and weight should be obtained, since growth retardation may be a manifestation of chronic renal disease, endocrine disorders, and other chronic illnesses. Blood pressure and peripheral pulses should be taken in both upper and lower extremities since differences in pressures and/or character of the pulse between arm and leg can be diagnostic of coarctation of the aorta. An abdominal examination should be performed, looking for masses (tumors, hydronephrotic or polycystic kidneys) and bruits (renal artery stenosis or abdominal coarctation). An examination of skin and musculoskeletal system should be performed looking for cafe-au-lait spots in neurofibromatosis; striae, acne, and hirsutism in Cushing's syndrome; ambiguous genitalia or virilization in adrenal hyperplasia; and joint pains and rash in systemic lupus erythematosis, to name just a few. Finally, a fundoscopic examination should be done to evaluate the severity and duration of the hypertension.

C. LABORATORY TESTS

The initial laboratory testing that is recommended in the evaluation of the child with hypertension is as follows: urinalysis, blood chemistries, hemoglobin/hematocrit, and an echocardiogram. These screening tests will often uncover an identifiable cause of the hypertension. If they do not, a decision must be made as to whether or not further evaluation and/or therapy should be undertaken. In patients with mild hypertension, close observation at frequent intervals is acceptable provided that significant cardiac hypertrophy is not present. However, when blood pressure levels are significantly elevated, further investigation is indicated.

1. Urinalysis

The urinalysis is used as a screening test to aid in the diagnosis of renal disease. Instead of obtaining just a spot urine, we recommend obtaining a urine specimen after overnight fluid restriction. After fluid restriction, a specific gravity of less than 1.025 is suggestive of either an inability to concentrate secondary to chronic renal disease, hypokalemia secondary to primary aldosteronism, or to a salt-wasting tubular defect. Such a finding requires that further renal studies, such as a renal technetium ^{99m}Tc scan, an intravenous pyelogram, or renal ultrasound, be performed. Hematuria of any degree and/or significant proteinuria are commonly seen in glomerular disease, whereas gross or microscopic hematuria alone may be seen in tumors or trauma to the urinary tract. White blood cells in the urine greater than five cells per high-power field or motile bacteria in fresh unspun urine indicate infection and should be confirmed by urine culture.

2. Blood Chemistries

Electrolyte abnormalities, particularly hypokalemia, can be seen in children with adrenal hyperplasia and primary hyperaldosteronism. Hyperkalemia is frequently seen in acute and chronic renal insufficiency. Metabolic acidosis is compatible with impaired renal function and tubulo-interstitial disease. The presence of both an elevated blood urea nitrogen and serum creatinine levels is an important predictor of a decreased glomerular filtration rate.

3. Echocardiogram

The last routine test is the echocardiogram. The echocardiogram is used not as an aid in establishing the etiology of the hypertension, but rather as an aid in the management of the hypertension (i.e., when to treat and how effective is the treatment in altering myocardial hypertrophy).[20]

4. Intravenous Pyelogram, Renal Ultrasound, and Renal Scan

The intravenous pyelogram allows assessment of both renal size and configuration of the upper portion of the collecting system. Symmetric decreases in kidney size are characteristic of chronic glomerulonephritis. Dilatation of the collecting system is seen in obstructive uropathy. Cortical scarring suggests chronic pyelonephritis. In addition, certain congenital disorders, such as polycystic disease of the kidney and the Ask-Upmark kidney, have characteristic radiographic appearance. Thus, the intravenous pyelogram may provide evidence of intrinsic renal disease or obstructive uropathy.

In recent years, renal ultrasound has replaced the intravenous pyelogram as the screening test of choice to define the gross anatomy of the kidney and ureters. As a routine screening procedure for the diagnosis of renovascular disease, the value of the intravenous pyelogram remains questionable.[21,22] Certain findings are suggestive of renal artery stenosis and may aid in a decision regarding angiography. Delayed appearance of contrast in the calyceal system of the affected kidney is an important sign of unilateral renal artery disease. Other findings include a difference in the size of the two kidneys of greater than 1 cm and hyperconcentration of the contrast in the pelvis and ureter of the affected kidney, as well as ureteral notching secondary to collateral vessels. Radionucleotide imaging using ^{99m}Tc dimercaptosuccinic acid along with complex computer analysis has recently shown great promise for the noninvasive screening of renovascular disease.[23,24]

5. Peripheral Plasma Renin Activity

Renovascular lesions, renal disease, or renin-secreting tumors may all be associated with elevated renin levels.[25,26] It must be emphasized that plasma renin activity should be interpreted in relationship to posture, time of day, and most importantly 24-h urinary sodium excretion.[27-29]

IV. CATEGORIZATION OF CHILDREN WITH HYPERTENSION

The data obtained from the combination of a good history and physical examination, the routine screening tests (urine analysis, blood urea nitrogen, creatinine, and electrolytes), and if necessary an intravenous pyelogram, renal ultrasound, renal scan, and plasma renin activity now allow one to categorize patients into four groups that require more specialized evaluation:

1. Group I consists of those children who have abnormalities indicative of renal disease. Either an ultrasound or intravenous pyelogram should be performed to demonstrate parenchymal and/or structural anomalies of the urinary tract. If the child has a history of recurrent urinary tract infections or dilatation of the ureters and collecting system and/or a decrease in kidney size and scarring on intravenous pyelogram, a voiding cystourethrogram is indicated to rule out ureteral reflux. The other invasive studies that may be indicated in this group of patients are cytoscopy, renal scan, and renal biopsy.
2. Group II consists of those children who have a history, physical examination, and/or screening tests which suggest a nonrenal cause for their hypertension. Further investigation should be aimed at the specific nonrenal cause such as measurement of 24-h urinary aldosterone, 17-ketosteroids, and glucosteroids in patients suspected of having mineralocorticoid abnormalities. Further measurement of urinary vanillylmandelic acid, catecholamines, and ^{131}I-metaiodobenzylguanidine scan[30] in patients suspected of having pheochromocytoma or specific cardiovascular studies in children suspected of having coarctation of the aorta should be undertaken.

TABLE 2
Drugs Used in Management of Hypertensive Crisis

Drug	Form	Dose	Interval	Onset
Diazoxide	i.v.	5 mg/kg/dose, rapid push	Q 3—24 h	1 min
Nitroprusside	i.v.	1—8 μg/kg/min	Continuous infusion	30 s
Hydralazine	i.v. or i.m.	0.15—0.5 mg/kg/dose, max 20 mg/dose	Q 3—6 h	15—25 min
α-Methyldopa	i.v.	5—10 mg/kg/dose, max 500 mg/dose	Q 4—8 h	1 h
Verapamil	i.v.	0.1 mg/kg followed by 1 mg/kg/h as a 5% glucose infusion (max 10 mg)	Bolus followed by continuous infusion	5 min
Nifedipine	Sublinguial	0.33 mg/kg	Q 4 h	30—60 min
Minoxidil	p.o.	0.2 mg/kg	Q 6 h	Within 1—4 h

3. Group III consists of those children who have normal screening studies except for an elevated peripheral plasma renin activity (greater than 2 SD above the mean for their 24-h urinary sodium excretion)[29] and/or a renal scan suggestive of renal vascular disease. Further studies will be necessary to both characterize and localize a possible renovascular lesion and to determine whether such a lesion may be amenable to either surgery or percutaneous balloon angioplasty. Further studies should include renal vein renins and renal arteriography.
4. Group IV consists of those children whose history, physical examination, and screening studies (including a renal ultrasound and peripheral renins) are normal. These children likely have essential hypertension; however, renal vascular disease is still a possibility. Our approach to these patients is to treat their hypertension if indicated and to perform renal vein renins and renal angiography if they do not respond readily to therapy.

V. MANAGEMENT OF SYSTEMIC HYPERTENSION

All children with significant, sustained hypertension and target organ damage should be treated. The treatment of hypertension can be divided into two major categories: hypertensive crisis and chronic hypertension.

A. HYPERTENSIVE CRISIS

Hypertensive crisis can be defined as life-threatening hypertension that is usually associated with either hypertensive encephalopathy and/or acute left ventricular failure. Table 2 lists drugs that can be used in the management of hypertensive crisis. The most frequent treatment of choice is an intravenous bolus of diazoxide given rapidly at a dose of 5 mg/kg, up to 300 mg, followed 1 h later by an intravenous dose of furosemide.[31] If one dose of diazoxide does not succeed in lowering the blood pressure, it may be followed by a second dose. If a second dose of diazoxide is not sufficient to control the blood pressure, it is then recommended to start a nitroprusside drip, beginning at a dose of 1 μg/kg/min, increasing until the blood pressure is satisfactorily controlled.[32] Recently, the calcium channel blockers, verapamil and nifedipine, have been reported to be very effective in the treatment of hypertensive crisis. Scharer and co-workers[33] reported that verapamil (0.1-mg/kg i.v. bolus followed by a constant infusion) was effective in treating hypertensive crises in 20 children (8 months to 16 years) with renovascular hypertension. The onset of action of intravenous verapamil was within 5 min, with maximal blood pressure lowering seen at 30 min and the duration of action greater than 1 h. Roth et al.[34] reported that sublingual nifedipine was effective in the treatment of 30 hypertensive emergencies in 20 children with renal disease. The mean dosage of nifedipine was 0.33 mg/kg. Strife and co-workers[35] have shown that a single oral dose of minoxidil (0.2 mg/kg) was effective in controlling severe hypertension in children with renal disease. These authors felt that the single oral dose of minoxidil not only obviated parenteral therapy, but also avoided the rapid, precipitous blood pressure changes that can occur with diazoxide or sodium nitroprusside. No matter what the agent used, once acute blood pressure reduction is achieved, other parenteral medicines need to be added in order to maintain long-term blood pressure control.

B. CHRONIC HYPERTENSION

The ideal treatment for chronic hypertension is to treat, if possible, the underlying disease responsible for the hypertension. If this is not possible, then nonpharmacologic and pharmacologic interventions are indicated.

1. Nonpharmacologic Management

Dietary management should be the initial form of therapy in all patients with hypertension. As can be seen from both our data and the work of Rames et al.,[7] obesity is present in at least 50% of the adolescents with essential hypertension. The treatment of choice for hypertension in these children is weight loss.[36-39] The most common treatment of obesity is caloric restriction in conjunction with behavior modification. We recommend a diet treatment which is designed to provide an acceptable dietary pattern which contains the necessary nutrients to promote growth, while allowing a weight loss of 1 to 2 lb/week.[40] We use the following method to devise the kilocalorie level to promote weight loss:

1. The calorie level currently maintaining the child's weight is derived by using food records kept for 6 days.
2. The child's daily calorie intake is then reduced by deducting 500 to 1000 calories.
3. In order not to impair growth, weight loss calorie levels are no lower than 1200 calories.
4. Weight loss calorie levels are no greater than 2500 calories, as higher calorie levels seem to promote cheating and the children do not take the diet seriously.

In addition to caloric restriction, behavior therapy intervention is mandatory. The purpose of the behavior therapy intervention is to help the child learn to eat as a normal-weight person, become aware of their current habits, and accept responsibility for their eating behavior through food behavior records. In addition to weight loss, dietary management of the hypertensive child should also attempt to reduce sodium intake. For a child who weighs 20 kg, this would provide approximately 1.25 g of sodium per day in the diet. Any attempts to institute a more stringent sodium restriction will probably fail since most children will find the food tasteless and intolerable.

In addition to dietary management, certain other nonpharmacologic measures should be included in the management of all hypertensive children. Child should be advised to avoid smoking, stop oral contraceptive pills and other vasoactive drugs, and avoid heavy alcohol consumption. In addition, daily physical activity of some kind should be encouraged. In relatively small groups of hypertensive patients, the resting blood pressures have been reported to be lowered, by 10 to 20 mmHg, after physical training.[41,42] Therefore, we recommend isotonic, dynamic exercise to all our patients with mild-to-moderate hypertension. Weight training has also been used for conditioning and has been shown to result in some blood pressure reduction.[43] However, the chronic effects of isometric vs. dynamic exercise on cardiovascular health remains controversial, since during isometric exercise both the diastolic and systolic pressures and heart rate increase and may produce unacceptable stress on the cardiovascular system.

2. Pharmacologic Management

With regard to pharmacologic management, the Second Task Force on Blood Pressure Control in Children has recommended that pharmacological management should be undertaken for children with severe hypertension (Table 1) in whom nonpharmacologic management has failed. In our institution, we are following these guidelines with the exception that if target organ damage is documented (i.e., cardiac hypertrophy on echocardiogram), we will institute medical management at a lower pressure.

Figure 3 lists our recommendations on blood pressure control in children. The stepped-care method represents a rational and uniform approach to treatment. Unlike the Task Force recommendations, we do not always use a diuretic as the initial drug in the antihypertensive regimen. In children who have a hyperdynamic circulation (i.e., tachycardia and wide pulse pressure) and/or an elevated plasma renin activity, we have found that a β-blocker, if not contraindicated, appears to be the best initial medication. If the child has diabetes, we feel that an angiotensin-converting enzyme inhibitor is the treatment of choice. Table 3 lists the dosage and some of the major side effects of a few of the commonly used antihypertensive agents. Antihypertensive medications can be divided into five major types: diuretics, adrenergic inhibitors, direct vasodilators, angiotensin-converting enzyme inhibitors, and calcium channel blockers.

VI. ANTIHYPERTENSIVE MEDICATIONS

A. DIURETICS

Diuretics are the most commonly used drug to treat hypertension.[44] Their major mechanism of action is to facilitate volume contraction by salt depletion. There are three major types of diuretics.

1. Benzothiadiazines

These drugs include hydrochlorothiazide, chlorthiazide, chlorthaladone, and metalazone. All of these drugs work in a similar fashion to block the reabsorption of salt and water in the proximal tubule.[45] Associated with the impaired reabsorption of sodium, there is also a proximal loss of bicarbonate and a distal loss of potassium.

Side effects of this class of diuretics include hypokalemia,[46] hyponatremia, hypercalcemia, hyperuricemia, thrombocytopenia, agranulocytosis, photosensitivity, gastrointestinal (GI) symptoms, parathesias, dizziness, weakness, and fatigue. The hypokalemia induced by these drugs may induce insulin resistance, which can precipitate diabetes in patients with glucose intolerance or worsen the degree of hyperglycemia in a patient with diabetes.[47,48] There is also indirect evidence that suggests that there may be a common mechanism for the glucose intolerance and the lipid abnormalities associated with diuretic therapy. Insulin resistance is believed to impair the utilization of glucose, increasing glucose levels and thereby interfering with the inhibitory effect of insulin on lipolysis. As a result, there is mobilization of fat which can result in an elevation of total serum cholesterol, low-density lipoprotein cholesterol, and triglyceride concentration, as well as a fall in the high-density lipoprotein cholesterol.[49] The increase in total and low-density lipoprotein cholesterol along with the decrease in high-density lipoprotein cholesterol is believed to raise the risk of coronary heart disease in patients treated with diuretics. In the diabetic patient, the thiazide diuretics are also associated with a higher glycosylated hemoglobin level.[49]

The thiazide diuretics are given orally and are rapidly absorbed from the GI tract. They are largely excreted intact by the kidney. The most commonly used drug in this class is hydrochlorothiazide and its standard dosage is 1 to 2 mg/kg/day, given in a twice-a-day format. Since these drugs have a flat dose-response curve, larger doses provide little additional antihypertensive effect, but will increase the fall in serum potassium.

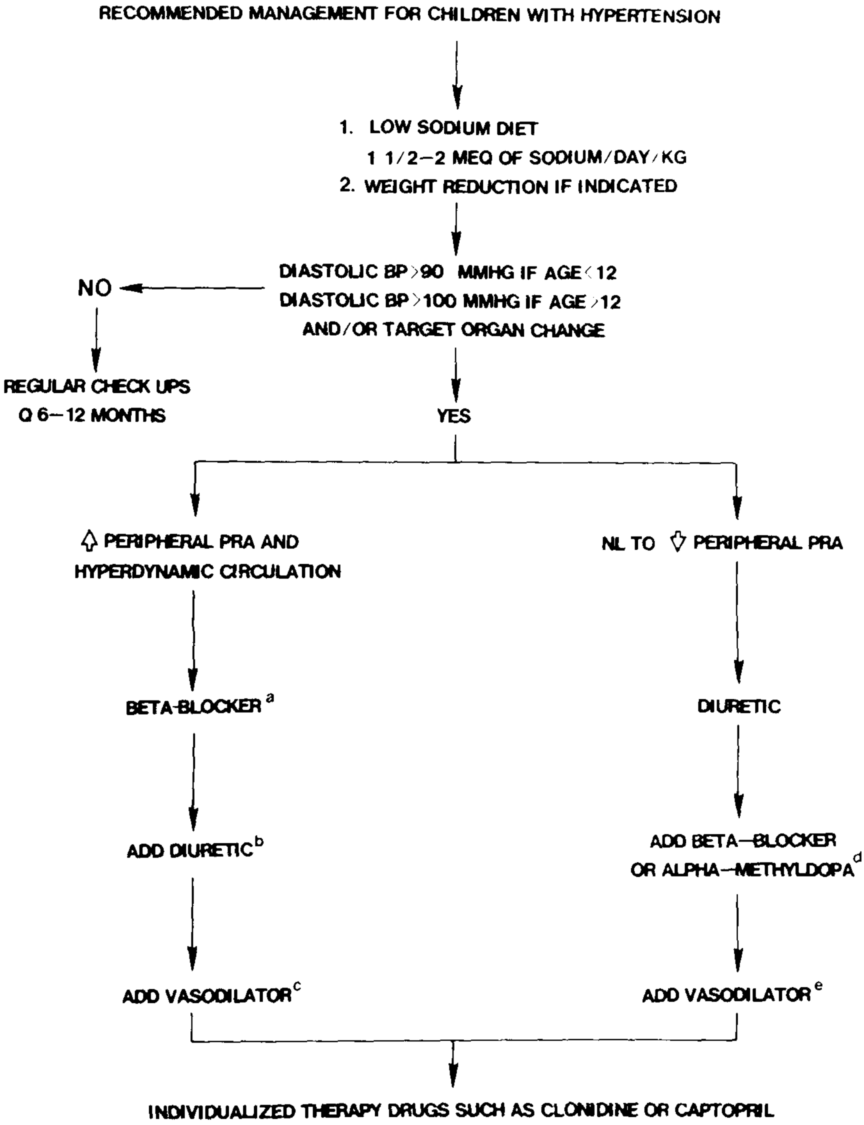

RECOMMENDED MANAGEMENT FOR CHILDREN WITH HYPERTENSION
1. LOW SODIUM DIET
1 1/2–2 MEQ OF SODIUM/DAY/KG
2. WEIGHT REDUCTION IF INDICATED
DIASTOLIC BP>90 MMHG IF AGE<12
DIASTOLIC BP>100 MMHG IF AGE>12
AND/OR TARGET ORGAN CHANGE
NO
REGULAR CHECK UPS
Q 6–12 MONTHS
YES
⇧ PERIPHERAL PRA AND
HYPERDYNAMIC CIRCULATION
NL TO ⇩ PERIPHERAL PRA
BETA-BLOCKER a
DIURETIC
ADD DIURETIC b
ADD BETA-BLOCKER
OR ALPHA-METHYLDOPA d
ADD VASODILATOR c
ADD VASODILATOR e
INDIVIDUALIZED THERAPY DRUGS SUCH AS CLONIDINE OR CAPTOPRIL

FIGURE 3. An approach to the management of the child with hypertension (abbreviations: PRA, plasma renin activity). (a) Propranolol and atenolol are our current drugs of choice; (b) hydrochlorothiazide, furosemide, aldactone, and chlorthaladone are our current drugs of choice; (c) hydralazine and minoxidil are our current drugs of choice; (d) α-methyldopa is used in place of a β-blocker if the child has a contraindication to the use of a β-blocker (i.e., asthma); if the child has insulin-dependent diabetes, then captopril is recommended. (From Rocchini, A. P., *Pediatr. Clin. North Am.*, 31, 1259, 1984. With permission.)

2. Loop Diuretics

These diuretics include furosemide, ethacrynic acid, and bumetanide. The principal site of action of this class of diuretics is on the ascending loop of Henle, where they inhibit chloride and secondarily sodium reabsorption.[45]

The major side effect of these drugs as with the thiazide diuretics is fluid and electrolyte depletion. In addition, hearing loss with or without tinnitus can occur with any of these agents, although it is more likely to occur with oral ethacrynic acid than the other two agents.[50] Unlike the thiazides, these diuretics can be given intravenously as well as orally. When given orally, these drugs are rapidly absorbed from the GI tract, causing a diuresis

TABLE 3
Oral Drugs Used in Management of Children with Hypertension

Drug	Starting dose (mg/kg/d)	Usual max dose	Interval	Mechanism	Main side effects
I. Diuretics					
Hydrochlorothiazide	1—2	2.75 mg/kg/d, 200 mg	BID	Salt and water depletion	K, CO_2, hyperuricemia, hyperglycemia
Furosemide	1—4	7 mg/kg/d	BID	Salt and water depletion	K, aldalosis, hyperuricemia, hyperglycemia, hearing loss, interstitial nephritis
Chlorthalidone	1	2 mg/kg/d 200 mg	qd	Salt and water depletion	K, aldalosis, hyperuricemia, hyperglycemia
Spironolactone	1	2 mg/kg/d, 200 mg	BID	Aldosterone antagonism	Gynecomastia, mental abnormalities, hyperhydrosis, ataxia, alopecia
II. Adrenergic Inhibitors					
A. β-Blockers					
Propranolol	0.5—2	16 mg/kg/d	BID or QID	β-Blockade	Hypoglycemia, HR, aggravates asthma, CHF, lethargy
Atenolol	0.5—1	100 mg	qd	β-Blockade	Cardioselective side effects like propranolol
Metoprolol	50—200 mg/d		qd or BID	β-Blockade	Relative cardioselective side effects like propranolol
B. Labetalol	100-200 mg/d[a]	1.2 g	BID	α- and β-Blocker	Dizziness, fatigue
C. Central-acting drugs					
α-Methyldopa	10—65 mg/kg/d, 4 g/d (max)		QID	Central-acting sympatholytic agent	Lethargy, fevers hemolytic anemia, hepatitis
Clonidine	0.005—0.01 mg/kg/d, 0.9 mg/d		BID or TID	Central α-agonist	Drowsiness, headache, nervousness, rebound hypertension
D. Peripheral inhibitors					
Guanethidine	0.2	2 mg/kg/d	BID	Peripheral ganglionic blockade	Orthostatic hypotension, drowsiness, depression
E. α-Blockers					
Prazosin	3 mg/d, 20 mg/d (max)		TID	α-Blocker	Syncope, tachycardia, headaches, arthralgias
III. Direct vasodilators					
Hydralazine	0.7—5 mg/kg/d		QID	Direct vasodilator	SLE syndrome, water retention, headache, tachycardia

Minoxidil	0.4—1.4 mg/kd/d, 50 mg (max)		QID	Direct vasodilator	Water retention, tachycardia, hypertrichosis, pericardial effusion
IV. Angiotensin-converting enzyme inhibitors					
Captopril	0.5—6 mg/kg/d		BID or TID	Blockade of the renin-angiotensin system	Neutropenia, rash, loss of taste, proteinuria, renal failure
Enalapril	10 to 40 mg[a]		BID	Blockade of the renin-angiotensin system	Like captopril
V. Calcium Channel Blockers					
Verapamil	4—6	10	TID	Calcium channel blocker	Bradycardia, constipation

[a] Adult dosage (no currently recommended pediatric dosage).

within 20 to 60 min.[51] The most commonly used drug in this class is furosemide and it is given in a dosage of 1 to 4 mg/kg/d.

3. Potassium-Sparing Diuretics

These drugs include spironolactone, triamterene, and amiloride. They work to enhance potassium reabsorption in the distal nephron. Side effects include gynecomastia, menstrual irregularities, hyperhydrosis, rash, drowsiness, ataxia, and alopecia. These drugs are well absorbed orally. The most commonly used drug in this class is aldactone and it is given in a dosage of 1 to 2 mg/kg.[52]

B. ADRENERGIC INHIBITORS

The second most common medication used as a first-line form of therapy in the treatment of hypertension is the adrenoreceptor inhibitor. The most popular drugs of this class of antihypertensives are the beta-blockers (β-blockers). The currently available β-blockers can be divided into major types: the cardioselective (including atenolol, metoprolol, acebutolol, and celiprolol) and the noncardioselective (including nadolol, pindolol, propranolol, and timolol). These medications work as sympathetic blockers and decrease cardiac output as well as renal renin release, but also appear to have CNS effects.[53]

Contraindications to the use of this class of agents is the presence of asthma, because of their β-II-blocking effect on the bronchiolar smooth muscle.[54] Another group of patients in which β-blockers can cause problems is children with insulin-dependent diabetes. In the diabetic patient, because of their deficient glucagon secretion, they rely mainly on epinephrine to promote recovery from hypoglycemia.[55] The β-blockers can block the ability of epinephrine to maintain blood sugar and increase the risk of hypoglycemia. The β-blockers also mask the signs and symptoms of hypoglycemia. During therapy with a β-blocker, the only sign of hypoglycemia that may remain is sweating.[57,58] β-Blockers as with diuretics have also been reported to alter lipid metabolism. It has been reported that β-blockers can cause triglycerides to increase and high-density lipoprotein cholesterol concentrations to decrease. Bradycardia is usually seen in conjunction with β-blockade; however, it is rarely significant enough to require decreasing the medication. Finally, lethargy, depression, and/or poor school performance can be a very serious problem associated with β-blocker therapy.

The most commonly used drugs in this class are propranolol and atenolol. Propranolol is well absorbed from the GI tract and is metabolized by the liver during its first passage with only one third reaching the systemic circulation. There is considerable interindividual variation in the amount of drug that is metabolized by the liver on the first pass and this contributes to the large differences in blood levels of the drug observed in different patients receiving the same dosage per kilogram.[58] The starting dose of propranolol is 1.5 to 2 mg/kg/d and this dose can be built up to 16 mg/kg/d. Atenolol is incompletely absorbed by the GI tract and is largely excreted unchanged in the urine. Atenolol has a plasma half-life of 6 to 8 h, but its antihypertensive action appears to last for a considerably longer period. It can therefore be given once a day. The initial dosage of atenolol is 0.5 to 1 mg/kg/d, with a maximum starting dosage of 50 mg.

A newly approved β-blocker that falls into its own class of adrenergic inhibitors is labetalol. Labetalol is interesting because it has α-blocking effects besides its β-blocking effect which theoretically increases its effectiveness as an antihypertensive agent. However, there is no information to date on its use in children.

A third class of adrenergic inhibitor drugs is the centrally acting drugs, including methyldopa, clonidine, guanabenz, and guanfacine. These drugs decrease peripheral vascular resistance through inhibition of central sympathetic outflow.[59-61]

Methyldopa has been used as an effective antihypertensive agent in the pediatric patient for a numbers of years. The most frequent side effects of methyldopa are sleepiness and lethargy which generally resolve with continued use of the drug, although these symptoms can be severe enough to require discontinuation of the medication. High fevers, Coombs positive hemolytic anemia, signs of liver damage, and diarrhea and other GI disturbances may also occur with use of this drug.[62,63]

Methyldopa is poorly absorbed from the GI tract and this probably explains the wide range of dosage required to achieve adequate blood pressure control. The drug is also excreted mostly from the kidneys.[63] The initial dosage of methyldopa is 10 mg/kg/d in a two or four times a day dose. The drug can be slowly increased to a maximum of 65 mg/kg/d or up to 4 g/d.

Clonidine is a central α-adrenergic agonist that reduces vasomotor activity in the medulla and thereby reduces heart rate and blood pressure. It has also been demonstrated to decrease adrenergic function and to inhibit the renin-angiotensin system.[64] There is also some experimental evidence to suggest that clonidine causes sodium and water diuresis due to both its central inhibition of antidiuretic hormone release as well as inhibition of tubular reabsorption of salt and water at the loop of Henle or proximal tubule.[65,66]

As with the other centrally acting antihypertensives, drowsiness is a common side effect. Dryness of the mouth can also be present. The most dangerous side effect, especially when used in adolescents, is that sudden cessation of clonidine therapy may cause a rebound phenomenon with a severe rise in blood pressure. This severe rise in pressure is associated with tachycardia, headache, nervousness, nausea, and increased secretion of norepinephrine.[67] Recently the acute administration of clonidine has been suggested as useful in the diagnosis of pheochromocytoma.[68,69] A dose of clonidine should suppress catecholamine secretion in those patients whose catecholamine secretion is centrally controlled, but not in patients with autonomous catecholamine-secreting tumors.

Clonidine is rapidly absorbed from the GI tract. Nearly one half of an oral dose of clonidine is metabolized in the liver and the other half is excreted unchanged in the urine.[70] The usual starting dosage of clonidine is 0.005 to 0.01 mg/kg/d in a twice-a-day dosage format. The drug can be increased to a maximum of 0.9 mg/d. Falkner and co-workers[71] have also demonstrated the effectiveness of transdermally administered clonidine in normalizing blood pressure in 22 adolescents. The advantage of transdermal clonidine is that the clonidine transdermal patch needs to be placed only once a week.[72] Guanabenz and guanfacine are other centrally acting antihypertensive agents that are used in adults, but there is limited information on their use in the child.

A fourth class of adrenergic inhibitors is the peripheral inhibitor, including reserpine, guanethidine, and guanidril. These drugs, although widely used several years ago, are rarely used today.

The final class of adrenergic inhibitor is the α-blockers prazosin and terazosin. Prazosin is not a direct vasodilator, but works by reducing peripheral vascular resistance secondary to blockade of α-adrenergic receptors. The blockade results in a reduction of vascular tone of both arterioles and veins. Since it is a selective α-I-blocker, tachycardia is not seen with its administration.[73]

Since first-dose orthostatic hypotension is seen with prazosin, the child should remain supine for 90 min and be watched for syncopal episodes. After the initial dose, syncope is uncommon.[74] The first-dose syncope can be avoided by stopping the administration of other antihypertensive drugs, particularly diuretics, 2 d before and 2 d after initiating prazosin therapy. Other side effects include headache, drowsiness, dry mouth, depression, rashes, urinary retention, and polyarthralgias.[75]

Prazosin is rapidly absorbed by the GI tract and is metabolized by the liver and excreted in the GI tract. To initiate therapy, a single dose of 1 mg should be tried. After the initial dose, the child can then be given 1 mg three times a day. The dose can be increased to a maximum of 20 mg/d.

C. DIRECT VASODILATORS

When a diuretic or an adrenergic inhibitor does not provide sufficient blood pressure control, the addition of a vasodilator may be effective in the majority of cases. The two major direct oral vasodilators are hydralazine and minoxidil. Both of these drugs are direct arteriolar vasodilators, thereby decreasing peripheral vascular resistance. Since these agents are accompanied by fluid retention and reflex tachycardia, they should always be administered concomitantly with a diuretic and β-blocker.

The metabolism of hydralazine depends on acetylation, and the inactivation of the drug may be decreased in "slow acetylators", and these patients may have increased side effects.[76] The side effects of hydralazine include flushing, nasal congestion, headache, dizziness, palpitations, and myocardial ischemia. Long-term therapy with large doses of hydralazine can lead to a lupus-like syndrome with positive antinuclear antibodies.[77,78] Hydralazine is rapidly absorbed from the GI tract and is metabolized by the liver. The oral dose of hydralazine varies from 0.7 to 5 mg/kg/d, with a maximum of 1.2 g/d. Hydralazine can be given intravenously at a dosage of 0.15 to 0.5 mg/kg per dose, with a maximum dose of 20 mg.

Minoxidil is generally used in children with severe refractory hypertension.[79] The side effects of minoxidil are sodium retention, tachycardia, hypertrichosis, and pericardial effusions. Excess body hair growth can be extremely bothersome to adolescents; however, it appears to be dose related and the body hair generally regresses within 4 to 6 weeks after stopping the medication. Pericardial effusions are usually associated with predisposing factors such as uremia, collagen vascular disease, or infections, but may be related solely to minoxidil therapy.[80] While not usually clinically significant in some patients, pericardial drainage or pericardectomy has been required. As with clonidine, reflex hypertension including hypertensive encephalopathy has occurred with rapid withdrawal. Minoxidil is rapidly and completely absorbed from the GI tract. It is metabolized by the liver and ultimately excreted by the kidney. The recommended dose of minoxidil is 0.1 to 0.2 mg/kg/d in a two to four times a day dosage format.[81]

D. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The angiotensin-converting enzyme inhibitors have in the past been solely used in children with severe and refractory hypertension. However, based on their safety and effectiveness, they are now becoming a first-line antihypertensive agent. In patients with diabetes, there is mounting evidence to suggest that they may be the drug of choice for the treatment of hypertension. At present, there are two drugs in this class that are currently approved for use: captopril and enalapril. The essential pharmacological effect of this class of antihypertensive agents is to inhibit the conversion of the relatively inactive angiotensin I to the active angiotensin II.[82] The advantage of the angiotensin-converting enzyme inhibitors over other antihypertensive agents is their ability to reduce efferent arteriolar resistance.[83] These drugs reduce the angiotensin II-mediated efferent arteriolar resistance to a greater degree than afferent arteriolar resistance, thereby reducing glomerular capillary hydraulic pressure. This effect is especially important in the diabetic patient since the angiotensin-converting enzyme inhibitors have been reported to reduce both proteinuria and the rate of decrease in glomerular filtration rate in these patients.[84] Other advantages of this class of antihypertensive medication are

1. The autoregulatory curve of cerebral blood flow is shifted downward, thus making it less likely for postural or other hypotensive symptoms to occur.
2. Tachycardia is not observed since there is no reflex sympathetic activation.
3. No fluid retention occurs, probably resulting from blockade of the angiotensin-mediated effect on aldosterone.
4. The angiotensin-converting enzyme inhibitors have little if any effect on carbohydrate or lipid metabolism.[85]

Captopril was the first drug of this class to be developed, and therefore the majority of the pediatric experience with this class of drugs has been with captopril. Mirkin and Newman[86] reported their results on captopril and found it to be an effective and safe drug for the treatment of children with severe hypertension. The reported side effects included hypotension, vomiting, anemia, rash, and anorexia. Leukopenia was reported in 6 of 73 patients, all of whom had severe renal impairment. A worsening of renal perfusion in the stenotic kidney of patients with renovascular hypertension is a rare problem, but may produce renal failure in those patients with bilateral disease or stenosis in a solitary kidney. Proteinuria may occur, especially in patients with a history of renal disease.

Captopril is rapidly absorbed from the GI tract and is excreted in the urine either unchanged as a disulfide dimer or as cysteine disulfide.[82] It is this disulfide metabolite which is believed to be responsible for many of the side effects of captopril. Satisfactory blood pressure control can usually be achieved with an initial dose of 0.05 to 0.1 mg/kg in infants less than 2 months of age. Older children should receive initial doses of 0.15 mg/kg with doubling of this initial dose over a 1- to 2-h period if the initial doses are ineffective. Thereafter, stepwise increments may be given, up to a maximal total daily dosage of 6 mg/kg, in older children with normal renal function. Patients with renal disease should receive reduced dosages of captopril. The suggested total daily dosage for maintenance therapy in adults is 450 mg for those with creatinine clearances above 80 ml/min/1.73m^2 and is adjusted to 300, 150, 75, and 37.5 mg for those with creatinine clearances of 41 to 80, 21 to 40, 11 to 20, and less than 10 ml/min/1.73m^2, respectively.[86]

Enalapril is a relatively new drug and there is limited experience with its use in the pediatric patient. Enalapril is reported to have several distinctive features.[87] It is more potent than captopril and has a prolonged duration of action which often allows effective treatment with a single daily dose. In contrast to captopril, enalapril is not a sulfhydryl compound and this may cause enalapril to produce less side effects than captopril. The incidence of rash and disturbance of taste appear to be lower than that reported for captopril; however, both neutropenia and proteinuria have been reported.

Enalapril is rapidly absorbed from the GI tract. Unlike captopril, enalapril is a prodrug and must be hydrolyzed to the active parent dicarboxylic acid, enaliprilate, before it is active. The daily dosage range for an adult has been reported to be from 10 to 40 mg, given once or in divided doses.

C. CALCIUM CHANNEL BLOCKERS

The calcium channel blockers have recently developed into a first-line drug for the treatment of hypertension in the adult patient. There is, however, only limited experience with the use of this class of antihypertensive agents in the pediatric age group. These calcium channel blockers are available in the U.S.: verapamil, nifedipine, and diltiazem. Unlike the β-blockers, the calcium channel blockers were developed from unrelated compounds. However, all of the calcium channel blockers have the ability to inhibit the flow of ionized calcium into cells. Their effect on vascular smooth muscle is to cause peripheral arteries and arterioles to dilate.[88] They have also been shown to cause glomerular flow rate and renal blood flow to increase, more so in patients who start with impaired renal function. In the adult population, the patients most likely to benefit from calcium channel blockers are blacks, the elderly, and the obese. Those patients with high systemic vascular resistance, high sodium intake, low renin level, low calcium intake, isolated systolic hypertension, and those with hypertensive crisis will also benefit.[89,90]

Verapamil was the first drug in this class to be approved for the treatment of hypertension.[91-93] The major side effects of verapamil are related to its cardiac effects on altering both cardiac contractility and impulse formation. As a result, verapamil can cause or aggravate congestive heart failure, sick sinus syndrome, and atrioventricular block. Other side effects include constipation, gastric upset, and urinary retention.

Verapamil is well absorbed from the GI tract; however, because of extensive first-pass metabolism by the liver, the bioavailability of the drug is low. Since verapamil is extensively metabolized by the liver, it should be administered cautiously in patients with severe liver disease or markedly reduced hepatic blood flow.[94] The dose of verapamil is 4 to 6 mg/kg. The typical adult dose is 240 to 480 mg in a three times a day dosage schedule.

F. AIMS OF TREATMENT

The goal of therapy is to keep the blood pressure below the 90th percentile for age and sex. Patients and/or their parents must be taught to monitor not only their (their child's) blood pressure at home, but also to monitor for signs of untoward side effects caused by drugs which they may be taking. Successful pharmacological therapy should not interfere with academic school performance, involvement in sports, or interest in social activities. Participation in team sports should be encouraged unless there is clear evidence of cardiac dysfunction with exercise stress tests. In addition, once the child's blood pressure is under good control, they should be evaluated at least on a yearly basis in order to evaluate cardiac status (echocardiogram) and physical growth and development, as well as patterns of sexual maturation.

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Chapter 7

PHARMACOLOGY AND TOXICOLOGY OF LOOP DIURETICS IN PEDIATRICS

Sam Kacew

TABLE OF CONTENTS

I. Introduction 142

II. Furosemide 142
  A. Pharmacological Actions 142
  B. Therapeutic Uses 143
    1. Respiratory Distress Syndrome 143
    2. Bronchopulmonary Dysplasia 144
    3. Patent Ductus Arteriosus 145
    4. Transient Tachypnea of Newborn 145
    5. Hydrocephalus 145
    6. Renal Tubular Acidosis 146
    7. Pregnancy 146
  C. Pharmacokinetics 146
  D. Adverse Effects 147
  E. Drug Interactions 148

III. Ethacrynic Acid 149
  A. Therapeutic Uses 149
  B. Pharmacokinetics 150

References 150

I. INTRODUCTION

By definition, agents which promote the secretion of water are classified as diuretics. In pediatrics, diuretics are utilized to mobilize edema fluid, thereby resulting in the production of a negative fluid balance and a return of extracellular fluid volume to a normal state. Regardless of whether the fluid overload state is due to etiological causes associated with cardiac, hormonal, renal, vascular, or pulmonary factors, there is an abnormal metabolism of water, the pathogenesis of which is not clearly understood. An excellent review describing the disease states associated with fluid overload and the management of these disorders was recently published by Aranda et al.[1] The particular emphasis in this review deals with furosemide; however, other diuretics are also effective in edematous states and will be considered in this chapter.

Disturbances in fluid balance can result in pathologic increases in fluid volume leading to edema and congestion. In neonatology a primary site for fluid accumulation is the lungs with a consequential development of pulmonary edema and congestive heart failure. Various factors can facilitate the accumulation of fluids in pulmonary tissue (Table 1). In association with pulmonary edema, there is an impairment in lung functions as outlined in Table 2. Pulmonary edema and lymphangiectasis are characteristic pathological alterations believed to play a role in the early stages of infant respiratory distress syndrome (RDS).[25,26] In addition the presence of a patent ductus arteriosus (PDA) was found to contribute to the development of RDS.[27] It has been suggested that a common sequela to RDS is the development of chronic lung disease or bronchopulmonary dysplasia (BPD).[28] Pulmonary edema has also been implicated in the disease transient tachypnea of the newborn (TTNB).[1] Clearly, there are a number of neonatal diseases associated with fluid imbalance which provide a basis for the therapeutic use of diuretics.

II. FUROSEMIDE

A. PHARMACOLOGICAL ACTIONS

It is well established that the predominant site of action of furosemide is on the thick ascending limb of the loop of Henle.[29] Based on this designated site of action, drugs in this class are referred to as loop diuretics. Pharmacologically, furosemide inhibits the reabsorption of sodium, chloride, and water.[30] Further, inhibition of sodium reabsorption in the proximal tubule attained a maximum at low doses of furosemide, while no maximum for inhibition of sodium reabsorption was reached in the distal tubule.[125] The furosemide-induced inhibition of proximal tubule sodium reabsorption is of short duration and accounts for the observed pharmacological peak. The finding that loop diuretics produce a peak diuresis that is far greater than that seen with other compounds has resulted in the designation of these drugs as high-ceiling diuretics. In addition, furosemide was shown to promote distal tubular secretion and excretion of potassium.[31] The enhanced excretion of electrolytes and fluid results in a reduction in extracellular fluid volume and, hence, mobilization of edema fluid regardless of the etiological cause.

In view of the known pharmacological properties of furosemide, this drug was initially used in pediatric practice in fluid overload conditions associated with either heart failure or pulmonary edema or the presence of both abnormalities. As early as 1964, Reimold[32] utilized furosemide to treat perinatal edema in the presence and absence of heart failure. Only in the infant with heart failure and pulmonary edema was there evidence of clinical improvement. Subsequently, furosemide was found to produce a significant diuresis and saliuresis in infants with fluid overload associated with congenital heart disease as well as in edematous states due to other causes.[33] Richardson[34] demonstrated that administration of furosemide to infants with heart failure or with pulmonary edema resulted in clinical improvement. The

TABLE 1
Factors Enhancing Lung Fluid Accumulation

Factor	Ref.
1. High fluid intake and patent ductus arteriosus	2, 3
2. Hypoxemia due to renal insufficiency or immaturity	4
3. Papillary muscle necrosis followed by left ventricular dysfunction	5, 6
4. Decreased serum protein levels	7
5. Oxygen toxicity	8
6. Elevated prostaglandin I_2 levels	9
7. Increased alveolar surface tension causing a shift of interstitial fluid to alveolar space	10
8. Increased concentration of plasma antidiuretic hormone	11, 12

Adapted from Yeh, T. F., Shibli, A., Leu, S. T., Raval, D., and Pildes, R. S., *J. Pediatr.*, 105, 603, 1984.

TABLE 2
Edema-Induced Consequential Pulmonary Abnormalities

Parameter	Ref.
High airway resistance	14, 15
Low dynamic pulmonary compliance	16, 17
Abnormal lung volumes	17, 18
Abnormal gas exchange	17, 18
Increased minute volume	15
Enhanced oxygen consumption	19
Lower pulmonary arterial pressure	20
Bronchial smooth muscle hypertrophy	21
Alterations in inflammatory-immune system	22
Radiographic appearance	23
Abnormal lymphatic clearance	25

Adapted from Kao, L. C., Warburton, D., Sargent, C. W., Platzker, C. G., and Keens, T. G., *J. Pediatr.*, 103, 624, 1983.

observed improvement was attributed to a marked excretion of water, sodium, and chloride and to a lesser extent, potassium excretion. Similarly, Ross et al.[35] administered furosemide to low-birth-weight infants with congestive heart failure. In addition to diuresis, natriuresis, and kaliuresis, the urinary pH was significantly decreased, indicating that furosemide was an effective diuretic for treatment of congestive heart failure and fluid overload. It is of interest that in infants and children with respiratory failure attributed to pulmonary edema, the furosemide-induced diuresis was associated with clinical improvement as evidenced by enhanced gas exchange.[36] Data clearly show that furosemide is an effective, potent diuretic in fluid overload conditions associated with congestive heart failure and pulmonary edema.

B. THERAPEUTIC USES
1. Respiratory Distress Syndrome

One of the etiological factors reported to occur in infant RDS is pulmonary edema[26] and this latter abnormality constitutes the rationale for the therapeutic use of furosemide. Moylan et al.[36] administered furosemide to infants and children with RDS ranging in age from 2 d to 15 years. Furosemide produced a significant increase in urine output accompanied by clinical improvement in the disease state as evidenced by correction of hypercapnea and improvement of hypoxemia. In a prospective study using 33 infants with RDS, the furosemide-induced diuresis was associated with a subsequent improvement in pulmonary function and beneficial effect especially in low-birth-weight infants.[37] In agreement with the suggestion that furosemide-stimulated diuresis is beneficial to RDS infants as evidenced by increased improvement in pulmonary function and oxygen use is the report by Belik et al.,[38] who indicated a change in the clinical course of the disease. In a recent study, the administration of furosemide was also found to enhance urine output, decrease the ventilatory mean airway pressure, and facilitate extubation in RDS premature infants.[13] Clearly, furosemide improved the pulmonary status in RDS infants, but failed to lower the incidence of morbidity and mortality, suggesting that the action exerted on the lung was not of clinical benefit. It is of interest that administration of furosemide to premature infants with RDS was also shown to increase the urinary excretion of sodium, calcium, and water.[39] However, in this study, Savage et al.[39] found no improvement in blood gas tensions. In a subsequent investigation, Marks et al.[40] demonstrated that the ability of furosemide to enhance urine output as well as sodium and calcium excretion in infants with RDS was related to a mobilization of subcutaneous fluid. Furosemide failed to mobilize pulmonary interstitial fluid and did not improve cardiopulmonary function.

At present there is a concensus that furosemide induces a diuresis in infants with RDS. However, a controversy exists as to the source of the mobilized fluid be it either pulmonary or subcutaneous. There is also a debate as to whether or not furosemide improves pulmonary function. To add to this dilemma is the suggestion that even in cases where pulmonary function is improved there is the finding that there is a lack of clinical benefit. In examination of the discrepancies in these studies, there is the inconsistency with respect to the duration of action of furosemide; a negligible effect was reported within 6 h where it is known that the onset of action occurs after 24 h.[13,37] A further problem is the knowledge that the newborn responsiveness to furosemide is extremely variable[41] which may account for the observed discrepancy in clinical improvement. It is thus generally recommended that furosemide not be administered on a routine basis to infants with RDS.

2. Bronchopulmonary Dysplasia

An important component in the development of bronchopulmonary dysplasia (BPD) or chronic lung disease is the presence of pulmonary edema. It is thus evident that the administration of furosemide to BPD infants has been advocated as a pharmacological manipulation to mobilize and reduce the fluid overload state. The observed pharmacological consequence would be expected to provide clinical improvement as evidenced by decreased respiratory difficulty. Indeed, Sniderman et al.[42,43] reported that furosemide treatment for 7 d produced an improvement in a clinical respiratory score in infants with BPD. Subsequent studies[44-46] revealed that furosemide administration to infants with mild BPD resulted in increased compliance and a decrease in airway resistance and respiratory rate, as well as a reduction in the alveolar to arterial oxygen gradient, indices of improved pulmonary mechanics and function. In agreement with these findings, Patel et al.[84] demonstrated an improvement in lung mechanics and gas exchange in infants severely affected with BPD. Kao et al.[24] found that within 1 h after furosemide treatment of infant BPD, there was a decrease in airways resistance associated with an increase in specific airway conductance and in dynamic pulmonary compliance. However, the observed improvement in pulmonary function was short lived, lasting only 24 h. In contrast, the furosemide-induced improvement in lung function was demonstrated after 4[44] and 7 d,[28] a point at which diuresis had already ceased. It was suggested that the improvement in pulmonary mechanics seen acutely with furosemide in BPD was related to diuresis, while the chronic action was due to a nondiuretic effect on lung vasculature.[28,44]

In a recent study, Engelhardt et al.[47] compared the short- and long-term effects of furosemide on lung function in infants with BPD. As reported by Kao et al.,[24] after 1 h furosemide only improved lung compliance. As furosemide therapy was increased to 7 d in spontaneously breathing BPD infants, there was a significant improvement in compliance and resistance, indices of lung mechanics. However, better oxygenation or gas exchange was only improved in 6 of 16 infants. Data thus suggest that furosemide is effective in improvement of lung mechanics, but this is not necessarily associated with clinical improvement as reflected by the failure to enhance gas exchange in more than half of the patients.[47]

The effectiveness of furosemide in improving lung function in infants with BPD after 7 d was unfortunately accompanied by the development of metabolic acidosis and worsening hypercarbia.[47] It is of interest that even in newborn rabbits with normal lungs, furosemide enhanced lung compliance by a decrease in lung water.[48] However, this was associated with metabolic alkalosis and reduced ventilation. Hazinski[48] suggested that the beneficial effects of furosemide usage for a prolonged period would not outweigh the risk of detrimental manifestations in BPD. This observation is borne out in the findings that chronic furosemide treatment results in renal calcification and bone disease.[49,50] In the therapy of infants with BPD, furosemide appears to be useful during intermittent periods of acute pulmonary edema.[1] Despite this apparent usefulness, Yeh et al.[13] found that furosemide did not significantly change the incidence of BPD in infants.

3. Patent Ductus Arteriosus

The relationship between RDS and the presence of a patent ductus arteriosus (PDA) is well known, and this latter complication occurs frequently in this respiratory disease in infants.[51,52] In infants with RDS and PDA, pulmonary function was further impaired as evidenced by increasing ventilatory and oxygen requirements,[27] and the PDA was a common sequela to BPD.[53] It is thus evident that fluid overload is associated BPD and RDS, of which PDA is increased in frequency, and, hence, furosemide is advocated for the treatment of PDA.[1,28] Green et al.[37,54] demonstrated that the furosemide-induced diuresis in infants with RDS and symptoms of PDA was associated with improvement in pulmonary function. Ironically, despite the beneficial effect of furosemide in infant RDS, the diuretic increased the incidence of PDA.[55] Green et al.[55] proposed that an elevation in prostaglandin E_2 synthesis might be responsible for the increased incidence of PDA. However, the beneficial effects of furosemide outweighed the risks in the treatment of RDS, as this diuretic did not produce a rise in mortality and morbidity due to PDA. In contrast, Yeh et al.[13] reported that furosemide did not appear to increase the incidence of PDA in infants with RDS. Regardless of whether or not furosemide affects the incidence of PDA in infant RDS, the question of clinical significance of chronic diuretic use still remains unresolved.

4. Transient Tachypnea of Newborn

A possible delay in the resorption of fetal fluid may result in the pathogenesis of a disease known as transient tachypnea of newborn (TTNB).[56] In general, TTNB is a benign and self-limited disorder accompanied by morbidity attributed to hypoxemia[57] and persistent pulmonary hypertension,[58] as well as pulmonary air leaks.[59] Since chest X-ray changes suggested that increased lung fluid played a role in the development of TTNB,[56,60] this finding provided the rationale for furosemide usage in this disorder. Wiswell et al.[61] administered furosemide to infants with TTNB. In comparison to control, furosemide failed to reduce the duration of hospitalization or the period of tachypnea in TTNB patients. Evidence thus suggests that furosemide does not appear to affect the clinical course of TTNB and seems to be an ineffective pharmacological tool for this disorder.

5. Hydrocephalus

One of the disorders advocated for the use of furosemide in conjunction with acetazolamide is posthemorrhagic hydrocephalus in infants.[62] Characteristically, these infants display a full anterior fontanelle, suture diastasis, prominent head veins, and rapidly increasing head circumference, indicative that hydrocephalus is secondary to intracranial hemorrhage.[63,64]

In a prospective study, Chaplin et al.[65] found that administration of furosemide and acetazolamide was effective as adjunct therapy to lumbar puncture to remove spinal fluid in the treatment of posthemorrhagic hydrocephalus. Although these infants did not require a permanent surgical shunt, successful removal of hydrocephalus was not associated with normal development as evidenced by poor IQ scores.[65,66] In addition to posthemorrhagic hydrocephalus, furosemide and acetazolamide have proved useful in the treatment of infants with myelomeningocele and hydrocephalus.[62,67] While a surgical shunt was avoided in the myelomeningocele population by means of pharmacological manipulation, the clinical improvement in neurological and cognitive processes was not determined. The mechanism responsible for the management of hydrocephalus by furosemide is believed to be related to the ability of this drug to reduce cerebrospinal fluid production.[68-70] However, it should be mentioned that the management of hydrocephalus with acetazolamide alone was found by other investigators to be ineffective.[71,72] It would thus appear that drug therapy of hydrocephalus should include a combination of furosemide and acetazolamide. Whether drug therapy is successful in providing clinical improvement still needs to be addressed.

6. Renal Tubular Acidosis

Type 4 renal tubular acidosis (RTA) is the most common form of RTA in children and is characterized by hyperchloremic acidosis, hyperkalemia, and a urinary acid pH.[73] Rather than a hypokalemia which is characteristic of Type 1 and 2 RTA, Type 4 is usually associated with aldosterone deficiency.[74] At present, the evaluation of the acidifying ability in the presence of Type 4 RTA is to administer an acid load; however, the preexisting hyperkalemia can be worsened to cardiotoxic levels.[75] In a recent study, Stine and Linshaw[76] demonstrated that administration of furosemide to an infant with Type 4 RTA and pseudohypoaldosteronism resulted in acidification of urine without an elevation in serum potassium. It is of interest that furosemide-induced urine acidification occurred in the presence of sodium bicarbonate, thus distinguishing Type 1 and 2 RTA from Type 4. The ability of furosemide to acidify urine and evaluate the presence of RTA has also been utilized in adults.[77,78] In the evaluation of the urine acidification ability in the infant with RTA, it appears that furosemide provides a safer approach than using an acid load.

7. Pregnancy

The use of furosemide during pregnancy for the treatment of maternal hypertension and edema is common.[79] Of particular relevance to the pediatrician is the knowledge that mothers taking furosemide during pregnancy inevitably affect the developing fetus and neonate. Administration of furosemide to pregnant mothers was reported to result in placental transfer of the drug accompanied by fetal uterine diuresis[80,81] and a decreased amniotic creatinine clearance.[82] Similarly, Vert et al.[83] demonstrated the transplacental transfer of furosemide from mother to fetus and noted an elevation in drug elimination rate with an increase in gestational age. However, these investigators[83] cautioned that in cases of intrauterine growth retardation, drug elimination rate would be considerably reduced. Further, at the early stages of gestation where furosemide tended to accumulate in amniotic fluid, the neonatal risk of dehydration and electrolyte loss would be higher. It is of interest that during delivery the maternal elimination of furosemide was abolished, which would further augment the fetal diuretic drug levels.[81] The consequences of maternal furosemide use to the fetus and newborn will be described later as part of Section II.D, Adverse Effects.

C. PHARMACOKINETICS

In view of the frequent and widespread use of furosemide in neonatal clinics,[1] attention has focused on studies to determine the pharmacokinetics of this drug in premature and full-term newborns. Parenteral administration of furosemide to newborns in general was shown to produce a diuretic effect within 1 h, and the duration of action was for 6 h.[35,41] It is of interest that the magnitude of the diuretic response was quite variable.[41] In comparing premature infants to newborns, the plasma half-life was considerably longer in the premature infant.[83,85] In agreement with this finding is the observation that elimination of furosemide is markedly slower in the neonate compared to the older child or adult.[86,87] Further, less furosemide is protein bound in newborns.[126] Indeed, the plasma half-life and elimination rate seen in newborns resemble that reported in adults with renal failure.[88] At present it is not established whether neonates with immature renal function accumulate furosemide to levels which may produce toxicity. However, it is evident that pharmacokinetic data warrant against frequent furosemide use in premature infants due to the slow elimination rate.

The major portion of furosemide administered to newborns is excreted unchanged.[87] With an increase in postnatal age, Aranda et al.[87] found the presence of urinary glucuronide and acid metabolites, suggesting that newborns also biotransform this diuretic, a metabolic phenomenon known to occur in adults.[89] The finding by Mirkin et al.[90] that phenobarbital reduced the pharmacological effectiveness of furosemide in infants clearly indicates that the diuretic action is subject to the capacity of the newborn to biotransform this compound. The precise role and relevance of furosemide metabolism to ultimate clinical improvement remain to be resolved in infants.

D. ADVERSE EFFECTS

It is generally accepted that the adverse effects of furosemide are directly attributable to the pharmacological actions exerted by the drug on the kidney. The furosemide-induced hypovolemia, poor tissue perfusion, and dehydration lead to a cascade of mineral imbalance abnormalities.[1,40] Notably, excess urinary electrolyte losses result in hyponatremia, hypokalemia, and hypochloremia. A clearly established side effect associated with chronic furosemide therapy is a hypochloremic, hypokalemic metabolic alkalosis.[1] In addition to sodium, potassium, and chloride, furosemide was reported to enhance the urinary excretion of calcium in adult patients.[91] Similarly, Hufnagle et al.[49] found that in preterm infants with chronic lung disease who were administered furosemide, a hypercalciuria developed. A consequence of this excess renal handling of calcium was attributed to the formation of renal calcifications, including isolated stones, staghorn calculi, and nephrocalcinosis. In agreement with these findings,[49] Venkataraman et al.[50] reported that the furosemide-induced renal calcification observed in preterm infants was accompanied by elevated serum parathyroid hormone. The increased levels of this hormone consequently resulted in abnormal bone mineralization and may lead to bone disease. It should be emphasized that with the use of a single dose of furosemide, Ross et al.[35] found no evidence of hyponatremia, dehydration, or electrolyte imbalance in infants.

Adverse effects attributable to furosemide utilization may be unrelated to electrolyte imbalance. In infants with respiratory distress syndrome, furosemide was found to increase the incidence of PDA.[55] Whitington and Black[92] demonstrated that furosemide produced cholelithiasis in preterm infants with BPD. The formation of gallstones in infants given furosemide was subsequently reported by other clinicians.[50] Furosemide was also found to displace bilirubin from albumin in newborn infants.[93] It is well established that neurotoxicity is associated with neonatal jaundice.[94] Thus, the potential for neurological abnormalities in jaundiced newborns administered furosemide chronically must be considered.[97] The duration of furosemide action is an important consideration as a single dose failed to displace bilirubin from the albumin-binding site.[86,95]

At present, it has been established that furosemide crosses the placental barrier.[81] However, the potential adverse effects on the fetus or postnatal human infant still need to be addressed. In rats, Mallie et al.[79] demonstrated that furosemide administration to pregnant animals produced a delay in renal maturation, as evidenced by a significantly lower number of differentiated glomeruli in the neonate. During the neonatal period and early infancy, renal function and excretion of drugs is not fully developed.[96] It is thus apparent that kidney function may be compromised to a far greater extent in infants of mothers taking furosemide during pregnancy.

E. DRUG INTERACTIONS

It should be reiterated that in a clinical setting an infant can be subjected to approximately five different drugs at the same time.[1] With respect to furosemide, this results in a whole host of adverse drug interactions and toxicity. One of the primary mechanisms responsible for the elimination of drugs is renal excretion, and furosemide by virtue of an action on the kidney ultimately affects this process. The renal clearance of practolol, an antihypertensive agent eliminated entirely by glomerular filtration, was reduced in adults administered furosemide.[98] It is thus evident that the concomitant use of furosemide and practolol in infants would also result in a prolonged duration of practolol action. Recently, Wilcox et al.[99] reported that furosemide administration in conjunction with prazosin and captopril lowered blood pressure in normal volunteers along with natridiuresis and kaliuresis. However, the finding that either prazosin[99] or captopril[100] alone lowered the blood pressure without effects on sodium or potassium was suggestive that furosemide acted independently of alpha-adrenoreceptors or the renin-angiotensin system. It is of interest that the interaction between furosemide and prazosin and captopril on blood pressure was not synergistic nor cumulative. Similarly, furosemide does not appear to affect the renal clearance of digoxin, indicating a lack of any significant interaction between these drugs.[101,102]

Although the interaction between digoxin and furosemide requires further study in children, it has been shown that furosemide in the presence of certain antibiotics produces serious consequences. Tilstone et al.[98] reported that furosemide decreased the renal clearance of gentamicin or cephaloridine in normal adults such that the antibiotic concentration attained in plasma was twice the amount required. It is thus not surprising that in neonates where renal function is still immature, the simultaneous use of furosemide and gentamicin results in nephrotoxicity and ototoxicity.[103,104] Similarly, concomitant administration of cephaloridine and furosemide was found to produce nephrotoxicity.[105] In contrast, indomethacin was reported to block the pharmacologic and toxicologic effects of furosemide.[114]

In certain conditions such as diuretic-resistant edema, the intentional use of several agents is a necessity. The current rationale is to employ drugs which exert a pharmacological action at different renal sites. Several investigators have thus administered furosemide in combination with metolazone, a diuretic which inhibits sodium reabsorption at the distal cortical and proximal convoluted tubule.[106] Unlike furosemide, metolazone has the least tendency to produce kaliuresis.[107] Epstein et al.[108] found that in adult patients suffering from cardiac, hepatic, or renal edema who failed to respond to furosemide alone, the addition of metolazone produced a prompt and substantial diuresis. Various investigators reported similar findings in adult patients refractory to furosemide, but suggested a diminution in furosemide dosage due to a development in neurotoxicity.[109,110] In children with a nephrotic syndrome resistant to furosemide, the addition of metolazone was found to achieve natriuresis.[111] In a more extensive study, Arnold[112] demonstrated that in furosemide-resistant edema in children, inclusion of metolazone produced an effective diuresis and natriuresis. However, combination furosemide and metolazone therapy was not effective in children with chronic renal insufficiency.[111,112]

Although not specifically related to infants and children, furosemide is believed to interact with a number of other drugs. As shown in Table 3, agents previously not mentioned also adversely interact with furosemide. The potential toxicity is heightened in the pediatric patient as renal function is still immature.

Furosemide is an important therapeutic agent when used properly. Excessive use will

TABLE 3
Furosemide Interactions with Other Drugs

Interacting agent	Adverse effect
Naproxen	Decreased diuresis and natriuresis
Indomethacin	Decreased natriuresis
Chloral hydrate	Vasodilatation and flushing
Clofibrate	Competes for binding to plasma albumin
Warfarin	Competes for binding to plasma albumin
Lithium	Increased lithium toxicity
Vancomycin	Ototoxicity
Phenytoin	Decreased diuresis and natriuresis
Corticosteroids	Hypokalemia

Adapted from Rizack, M. A. and Hillman, C. D. M., Eds., *The Medical Letter Handbook of Drug Interactions,* Medical Letter, New Rochelle, NY, 1983, 60.

result in an increased incidence of adverse effects. Should furosemide therapy be unsuccessful in elimination of the disorder, it is not prudent to increase furosemide utilization, but to attempt a different form of treatment be it surgery or an agent acting at another renal locus. The clinician should be aware that furosemide affects the pharmacological and toxicological actions of other drugs. Furosemide drug interactions are probably worsened in the pediatric patient where renal function is not fully developed.

III. ETHACRYNIC ACID

In 1963, a ketone derivative of phenoxyacetic acid, ethacrynic acid, was introduced into clinical practice.[115] Ethacrynic acid was utilized as a potent diuretic in adults for fluid retention states associated with cardiac, renal, or liver disease.[116,117] As in the case of furosemide, ethacrynic acid exerts a natriuresis and diuresis, primarily via an action on the ascending limb of the loop of Henle. An extensive review by Cannon and Kilcoyne[118] describes in detail the pharmacologic and toxicologic, as well as therapeutic indications for ethacrynic acid in adult patients.

A. THERAPEUTIC USES

The therapeutic roles of ethacrynic acid in pediatrics are similar to that reported for the adult. In both age groups, the popularity of furosemide greatly exceeds that of ethacrynic acid. Indeed, in a neonatal intensive care unit, Aranda et al.[87] found that 24% of infants were exposed to furosemide, while only 3.6% of neonates were subjected to ethacrynic acid. In light of the fact that ethacrynic acid is available for usage by the pediatrician, the known reports of this agent will be discussed. James[119] administered ethacrynic acid to edematous children with either acute nephritis, nephrotic syndrome, or congestive heart failure. In all cases, ethacrynic acid produced a diuresis and weight loss; however, the tendency to induce a hypochloremia and alkalosis suggested that the use of this drug be restricted to hospitalized children.

Although the therapeutic benefit derived from ethacrynic acid use in infants with acute glomerulonephritis was questioned,[119] Sparrow et al.[120] reported a significant diuresis and clinical improvement in all children with congestive heart failure after administration of this diuretic. The observed diuresis was rapid, did not change serum electrolyte concentration, and failed to produce any apparent side effects. Similarly, Willard and Geisett[121] found that ethacrynic acid was effective in the treatment of congestive heart failure in newborns. Thus, it is apparent that ethacrynic acid is of therapeutic benefit in the therapy of fluid overload associated with congestive heart failure in infants and is of questionable value in idiopathic edema in newborns.

B. PHARMACOKINETICS

Despite the longevity of ethacrynic acid in the marketplace and the limited usefulness of this agent in pediatric patients, virtually little is known about the pharmacokinetics of this diuretic in neonates. The active form of ethacrynic acid is an ethacrynic-cysteine complex which must be present in the tubular lumen to exert a pharmacological action.[122,123] Scalais et al.[124] administered ethacrynic acid to neonates with fluid overload states, including bronchopulmonary dysplasia, respiratory distress syndrome, patent ductus arteriosus, or respiratory distress syndrome. Within 1 h after intravenous administration, ethacrynic acid increased the excretion of sodium, chloride, potassium, and calcium, and this observed diuretic effect lasted for approximately 5 h. Of the ten newborns given the diuretic, only two developed a mild hyponatremia. In contrast, the onset of action as well as duration is shorter in the adult administered ethacrynic acid.[118] Scalais et al.[124] concluded that ethacrynic acid displays a prolonged diuretic and saluretic action in the neonate. The potential consequences for electrolyte imbalance should thus be borne in mind when utilizing ethacrynic acid in a neonatal intensive care unit. Clearly, further investigation is necessary with respect to toxicity, drug interactions, etc. in the case of ethacrynic acid use in pediatrics.

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Chapter 8

CHLORAMPHENICOL

Steven R. Abel and Martin B. Kleiman

TABLE OF CONTENTS

I. Introduction 156

II. Chemistry 156

III. Mechanism of Action 156

IV. Antimicrobial Activity 157
  A. *In Vitro* Activity 157
  B. Bacterial Resistance 157
  C. Antagonism of Bactericidal Antibiotics 159

V. Assay Methodologies 159

VI. Pharmacokinetics 160
  A. Absorption and Bioavailability 160
    1. Chloramphenicol Base 160
    2. Chloramphenicol Palmitate 160
    3. Chloramphenicol Succinate 160
  B. Distribution 161
  C. Metabolism 162
  D. Excretion 163
  E. Half-life 163
  F. Effect of Concomitant Disease States 163
    1. Hepatic Dysfunction 163
    2. Renal Dysfunction 164
    3. Shock 164

VII. Toxicity 164
  A. Hematologic 164
  B. Gray Baby Syndrome 165

VIII. Dosing 167

IX. Therapeutic Monitoring 168

X. Current Indications for Clinical Use 168

XI. Summary 169

Acknowledgment 169

References 169

I. INTRODUCTION

Isolated from *Streptomyces venezuelae* in 1947, chloramphenicol was first marketed in 1949. Its use quickly became widespread due to its broad spectrum of antimicrobial activity. While knowledge of its suppressive effects on the bone marrow became evident within 3 years of its introduction, the first report of the gray baby syndrome was not published until 1959.[1] Thereafter, recognition and concern regarding life-threatening side effects substantially curtailed the use of chloramphenicol, especially oral preparations, until the emergence of ampicillin-resistant *Haemophilus influenzae* type b infections in 1973. Currently, chloramphenicol maintains a niche, although new drugs have been developed which continue to narrow the indications for chloramphenicol as a drug of first choice.[2] This chapter will review the antimicrobial spectrum, pharmacokinetics, toxicity, dosing, recommendations for therapeutic monitoring, and current clinical indications for chloramphenicol.

II. CHEMISTRY

Chloramphenicol, acetamide, 2,2-dichloro-*N*-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl], is unique among naturally occurring compounds in that it contains a nitrobenzene moiety and is a derivative of dichloroacetic acid (Figure 1).[2] When this relatively simple molecular configuration was first described, it was anticipated that antimicrobial properties might be augmented and toxic characteristics eliminated by chemical alterations of the basic structure. One product of this alteration was thiamphenicol, an analog in which a methyl sulfone is substituted at the position occupied by a nitro group in the parent compound.[3] To date, no reports have been published associating thiamphenicol with aplastic anemia.

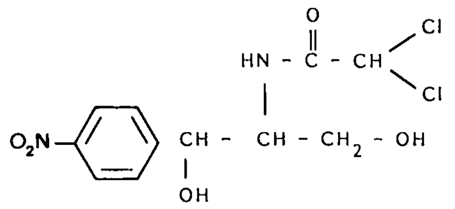
Chloramphenicol is an extremely stable, lipid-soluble compound which is most soluble in organic solvents; it is poorly soluble in water with a maximum solubility of only 4 mg/ml.[2,3] The compound resists degradation by a variety of physical and chemical factors such as pH, light, and temperature. Chloramphenicol is inactivated by enzymes which are found in filtrates of some bacteria and which reduce the nitro group and hydrolyze the amide linkage.[2]

Chloramphenicol is available for oral administration, either as the base, a bitter-tasting powder marketed in capsules, or as an inactive prodrug, chloramphenicol palmitate, marketed as a tasteless oral suspension. Following oral administration, chloramphenicol palmitate is hydrolyzed to active chloramphenicol by pancreatic lipases in the duodenum.[4] Chloramphenicol succinate, also an inactive prodrug, is available for parenteral administration. This salt is hydrolyzed to active chloramphenicol by esterases in the liver, kidneys, and lungs.[2,5]

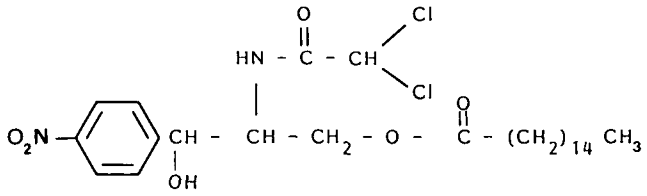
III. MECHANISM OF ACTION

Chloramphenicol acts to inhibit protein synthesis in susceptible organisms by reversibly binding to the 50 S ribosomal subunit of bacterial 70 S ribosomes. Chloramphenicol may inhibit peptide bond formation by suppressing peptidyl transferase activity.[6] The binding takes place at a single ribosomal receptor which is competitively inhibited by lincomycin, clindamycin, or macrolide antibiotics.[2]

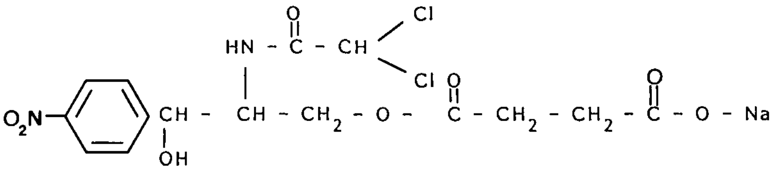
Chloramphenicol can also inhibit mitochondrial protein synthesis in mammalian cells, particularly those with rapid proliferation.[2,6] This may occur because mitochondrial ribosomes resemble bacterial ribosomes (both are 70 S) more than they do the 80 S cytoplasmic ribosomes of mammalian cells.[2] Mammalian erythropoeitic cells seem to be particularly sensitive to the drug.[2,6]



Chloramphenicol



Chloramphenicol palmitate



Chloramphenical sodium succinate

FIGURE 1. Chloramphenicol and its salts.

IV. ANTIMICROBIAL ACTIVITY

A. *IN VITRO* ACTIVITY

Chloramphenicol demonstrates a broad spectrum of antimicrobial activity against a variety of organisms, including bacteria, spirochetes, rickettsia, chlamydiae, and mycoplasmas. The *in vitro* susceptibilities of common bacterial isolates are given in Table 1. Isolates are considered susceptible if their growth is inhibited by concentrations of 12.5 μg/ml or less[7] and if they are nonproducers of chloramphenicol acetyltransferase.[8] While considered to be primarily bacteriostatic, chloramphenicol has exhibited bactericidal activity against certain organisms which are common causes of meningitis in children, including *H. influenzae* and *Streptococcus pneumoniae*.[2,9] A third common pathogen in childhood meningitis, *Neisseria meningitidis*, is usually susceptible, but concentrations of up to 50 μg/ml have been required for bactericidal activity.[9] The drug is bacteriostatic against most salmonella, staphylococci, and streptococci.[10] In the U.S., resistant strains occur, but imported strains may be highly resistant.[11,12]

B. BACTERIAL RESISTANCE

The *in vivo* resistance of microorganisms usually susceptible to chloramphenicol, especially *H. influenzae* and salmonella, is an increasingly difficult problem.[2,13] A U.S. multicenter study of more than 3000 clinical isolates of *H. influenzae* found 0.6% to be chloramphenicol resistant.[14] Jones and Thornsberry[15] have expressed concern that this rate of resistance may be greater with the use of more appropriate interpretive criteria. Of greatest concern have been reports of a strain of *H. influenzae* type b, resistant to chloramphenicol and ampicillin.[13,16] Such organisms have accounted for deaths of children in Thailand where

TABLE 1
Sensitivities to Chloramphenicol of Bacterial Isolates Obtained from Patients at Indiana University Hospitals, 1985

Organism	Number of strains	Percentage susceptible to chloramphenicol[a]
Gram-negative organisms		
Acinetobacter anitratus	23	9
Acinetobacter iwoffii	16	60
Citrobacter diversus	35	86
Citrobacter freundii	51	80
Enterobacter aerogenes	120	78
Enterobacter cloacae	146	77
Escherichia coli	890	69
Haemophilus influenzae	15	100
Klebsiella oxytoca	81	86
Klebsiella pneumoniae	298	82
Morganella morganii	37	78
Proteus mirabilis	225	88
Proteus vulgaris	35	54
Pseudomonas aeruginosa	458	2
Pseudomonas maltophilia	16	50
Pseudomonas sp. (other)	18	17
Salmonella enteritidis	13	92
Serratia marcescens	80	11
Gram-positive organisms		
Staphylococcus aureus	501	100
Staphylococcus coagulase negative	554	90
Enterococcus sp.	414	88
Anaerobic organisms		
Bacteroides fragilis	24	100
Bacteroides thetaiotaomicron	82	96
Bacteroides vulgaris	41	100
Bacteroides distasonis	31	100
Bacteroides intermedius	10	100
Bacteroides melaninogenicus	38	100
Bacteroides bivius	36	100
Fusobacterium mortiferum var. *F.*	8	100
Fusobacterium necrophorya	16	100
Fusobacterium nucleatum	116	100
Actinomyces sp.	9	100
Clostridium perfringens	67	100
Clostridium ramosum	27	100
Clostridium difficile	127	100
Clostridium septicum	11	100
Propionibacterium acnes	388	100
Peptostreptococcus anaerobius	88	100
Peptostreptococcus magnus	178	98
Peptostreptococcus prevotii	99	100
Streptococcus intermedius	25	100
Veillonella parvula	76	100

[a] MIC was ≤ 8 μg/ml.

47% of *H. influenzae* type b strains isolated from the nasopharynx of 38 children were found to be resistant to both drugs.[16,17] The emergence of chloramphenicol-resistant strains of salmonella, sometimes during treatment, is also of clinical significance.[11] Strains of *Salmonella typhi* and *Shigella dysenteriae* resistant to chloramphenicol have caused epidemic disease in Mexico and Central America in the early 1970s.[11,16]

Bacterial resistance to chloramphenicol may be mediated by a variety of mechanisms. Resistance in many Gram-negative bacteria may be due to an R-factor encoding for acetyltransferase. This enzyme acetylates the hydroxyl group side chain to the inactive diacetyl derivative.[12,18] This mechanism of resistance occurs in *H. influenzae*, in which the plasmid sometimes also encodes for beta-lactamases which confer ampicillin resistance. Plasmid-mediated resistance by conjugation has been demonstrated between strains of *Haemophilus* and from *Haemophilus* to other Gram-negative bacteria.[19] Resistance among certain strains of *Pseudomonas* and *Serratia* may be transmitted chromosomally.[16,20] Other mechanisms of chloramphenicol resistance include relative impermeability of cells (*Escherichia coli* and *Pseudomonas*), and ribosomal insensitivity.[21]

C. ANTAGONISM OF BACTERICIDAL ANTIBIOTICS

Chloramphenicol has been shown to inhibit the early, rapid killing effect of penicillin *in vitro* for *Streptococcus pyogenes* and *Klebsiella pneumoniae*.[22] Chloramphenicol had to be administered a half hour to an hour prior to the penicillin in order to demonstrate antagonism. This antagonism may be explained by the observation that chloramphenicol may inhibit bacterial autolytic enzymes that contribute to rapid bacterial killing in the presence of penicillin.[23] However, other *in vitro* studies have demonstrated synergism between penicillins and chloramphenicol.[24,25] Chloramphenicol inhibited the rapid bactericidal effect of gentamicin against strains of *E. coli in vitro*, but did not have this effect for anaerobes, including *Bacteroides fragilis*.[26]

Two clinical studies have reported possible antagonism between penicillin and chloramphenicol for the treatment of meningitis. Mathies et al.[27] reported a 6.2% increase in deaths (6 of 140 patients vs. 13 of 124 patients) of patients treated with ampicillin alone vs. ampicillin, chloramphenicol, and streptomycin. Lindberg et al.[28] reported an increase in eighth cranial nerve sequelae in children with *H. influenzae* meningitis when treated with ampicillin and chloramphenicol compared to children receiving ampicillin alone. Mortality was equal in both groups.

V. ASSAY METHODOLOGIES

An understanding of available assay methodologies utilized to measure chloramphenicol serum levels is essential to interpret susceptibility data, assess pharmacokinetics, and interpret studies of chloramphenicol usage. Methods used for quantitation of chloramphenicol include bioassay and chemical (colorimetric), radioenzymatic, gas liquid chromatographic (GLC), and high-performance liquid chromatographic (HPLC) assays, each with its advantages and disadvantages.

Bioassays require long incubation times, are less reproducible, and are affected by interference with other antibiotics in the samples.[29] Chemical or colorimetric methods measure free drug as well as the amine formed after reduction of aromatic nitro groups of chloramphenicol.[30,31] The inactive prodrug and the glucuronide metabolite containing nitro groups thus interfere with measurement. While the radioenzymatic assay is rapid, precise, sensitive, and specific, disadvantages of this assay include high cost and inability to measure the prodrug or drug metabolites.[31] Gas chromatographic assays are accurate, precise, sensitive, and specific, but methodologies are complicated and require derivatization of the drug before separation and quantitation.[29,31] HPLC methods have been shown to be precise and sensitive and to measure the free drug, as well as chloramphenicol succinate and the major glucuronide metabolite.[29,32] HPLC is currently the method of choice for measurement of chloramphenicol levels.[31] Nahata[31] has prepared a useful comparison of the five analytical techniques available for routine monitoring of chloramphenicol serum levels.

VI. PHARMACOKINETICS

A. ABSORPTION AND BIOAVAILABILITY

Assessment of the absorption and bioavailability of chloramphenicol varies with the preparation administered (base, palmitate, or succinate ester).

1. Chloramphenicol Base

Roy et al.[33] reported that administration of oral chloramphenicol powder mixed in a small amount of sugar solution and given to 14 children was followed by peak plasma concentrations 2 to 4 h after a single dose. Multiple oral doses at 4-h intervals resulted in irregular absorption, which the authors attributed to difficulties in administration and/or retention in the gastrointestinal (GI) tract. Glazko et al.[34] demonstrated that the rate and extent of oral absorption of chloramphenicol from capsules differed from one product to another. Preparations with small particle sizes and therefore larger surface areas may have faster rates of absorption. However, the ultimate extent of absorption of small-particle-size chloramphenicol is equivalent to products having larger particle sizes.[34,35] Glazko et al.[34] reported bioavailabilities of 76 to 93% with chloramphenicol base preparations; for products with rapid dissolution and deaggregation rates, peak concentrations occurred 0.5 to 2 h after a dose.

2. Chloramphenicol Palmitate

Chloramphenicol palmitate (Figure 1) is hydrolyzed in the duodenum to active chloramphenicol by pancreatic lipases.[4] Glazko et al.[36] demonstrated that chloramphenicol palmitate was hydrolyzed more rapidly and was better absorbed than chloramphenicol stearoylglycolate. Utilizing assessment of urinary excretion of aryl nitro compounds, the bioavailability of chloramphenicol from the palmitate ester was 78.6% compared to 72.4% for the steroylglycolate. The bioavailability of chloramphenicol palmitate administered orally to infants and children has been found to exceed that of intravenously administered chloramphenicol succinate.[37-39] Shankaran and Kauffman[40] determined that increases in dosage from 25 to 50 mg/kg/d of chloramphenicol palmitate were required in preterm neonates to achieve adequate serum levels. Although palmitate ester bioavailability is equal or superior to that of the parenteral succinate ester in older infants and children, the palmitate ester appears to be less bioavailable in neonates.[40] In a study of premature infants from 24 to 29 d of age, blood levels of chloramphenicol averaged 22.6 μg/ml[41] 6 h after a 50-mg/kg dose of chloramphenicol palmitate. Similar dosing resulted in peak serum levels at 4 h in infants and at 2 h in older children.[41] Other investigators have observed peak serum concentrations 2 to 3 h after administration of chloramphenicol palmitate to infants and children.[36-39,41] Ross et al.[42] observed that concentrations were higher for the first 2 h following administration of chloramphenicol palmitate in the fasting state, but were comparable to postprandial administration 4 to 8 h following a dose.

3. Chloramphenicol Succinate

The succinate ester of chloramphenicol (Figure 1) is the inactive prodrug for parenteral use. Chloramphenicol succinate is hydrolyzed to free chloramphenicol in the liver, lungs, and kidney. The incomplete bioavailability of chloramphenicol succinate results from renal excretion of the chloramphenicol ester, thereby reducing the amount available for conversion to active drug.[35,43] Nahata and Powell[44] administered chloramphenicol succinate (25 mg/kg) to 12 patients ranging from 2.5 months to 20 years of age and found the bioavailability to range from 55 to 92%. The bioavailability of chloramphenicol, therefore, is a function of both the rate and extent of metabolism (hydrolysis) as well as the renal excretion of chloramphenicol succinate.[4,35,44-47]

Nishimura and Kotani[41] observed two distinct peak concentrations, at 1 and 4 h, after administration of 25 mg/kg of chloramphenicol succinate to premature and term newborns. The 4-h levels were higher in patients up to 13 d of age, but were not seen in infants and older children. The authors suggested that the two peaks resulted from a reduced rate of glucuronic acid conjugation in the liver of premature/newborn infants.

Rajchgot et al.[48] found an initial dose of 12.5 mg/kg of chloramphenicol succinate inadequate to achieve serum concentrations greater than 10 μg/ml in 45% of premature neonates. They found that an initial dose of 20 mg/kg was required to achieve therapeutic serum levels (mean of 15.9 μg/ml). The disposition of chloramphenicol was age dependent, with peak concentrations at 4 h in newborns 2 d old or less and 2 h in neonates 3 to 55 d old. Chloramphenicol succinate concentrations at 2 and 4 h after a dose were higher in younger neonates. The authors suggested that renal excretion was probably not a major factor in chloramphenicol succinate disposition in the neonate because renal function was underdeveloped in newborns. However, whether the delayed rise of serum chloramphenicol concentrations seen in this group was related to slower hydrolysis or a prolonged distribution phase could not be determined. In contrast, Nahata and Powell[49] studied the comparative bioavailability of chloramphenicol in premature infants 5 to 13 weeks old, full-term infants 2.5 to 12 months old, and children older than 1 year. Mean bioavailability was 93% in premature infants, 71% in full-term infants, and 64% in children. The authors concluded that the increased bioavailability of chloramphenicol in premature infants was associated with decreased renal clearance of chloramphenicol succinate.

Intramuscular administration of chloramphenicol succinate has not been recommended, and data which examined drug availability are conflicting. DuPont et al.[50] reported lower plasma levels, delayed clinical response, and high relapse rates with intramuscular vs. oral administration. Two additional studies reported that intramuscular administration was followed by peak plasma levels and areas under the plasma level curves that were not significantly different than those following intravenous administration.[45,51]

B. DISTRIBUTION

Owing to its lipid solubility, chloramphenicol is widely distributed throughout the body. Varying concentrations of chloramphenicol have been found in aqueous humor, breast milk, semen, pleural, and ascitic fluid.[31,35,41,52] Koup et al.[53] reported a significant but variable relationship between serum and saliva chloramphenicol levels. It was found that saliva chloramphenicol concentrations could not be used to assess serum concentrations. Highest tissue concentrations occur in the liver and kidney, while the lowest are found in the brain and cerebrospinal fluid (CSF).[3,31] Average CSF values range from 20 to 99% of concomitant serum levels.[33,37,38,54-57] Yogev et al.[38] found trough serum levels significantly higher after oral administration as compared to intravenous injection. However, the CSF to blood ratios were similar after each route of administration.

Chloramphenicol is efficiently distributed to the fetus. Oral dosages of 2 g resulted in fetal cord blood concentrations which were 86% of simultaneous maternal serum levels.[58] Oral dosages of 1 or 2 g resulted in placental concentrations of chloramphenicol which were 30 to 80% of maternal levels.[59]

The mean protein binding of chloramphenicol was 53% in normal adults, 42% in cirrhotics, and 32.4% in premature infants.[60] Sack et al.[61] reported a mean volume of distribution of 1.39 ± 0.34 l/kg in 17 children aged 1 month to 6 years. However, this study assumed complete hydrolysis of chloramphenicol succinate to chloramphenicol such that volumes of distribution may have been overestimated.[31] Mean apparent volumes of distribution were 0.71 l/kg for chloramphenicol and 2.10 l/kg for chloramphenicol succinate in 12 children aged 2.5 to 20 months.[44] The mean volumes of distribution for five premature infants (5 to 13 weeks old) were 1.55 ± 0.67 and 0.76 ± 0.65 l/kg for eight full-term infants (aged 2.5 to 12 months) and 0.63 ± 0.29 l/kg for four children over 1 year of age.

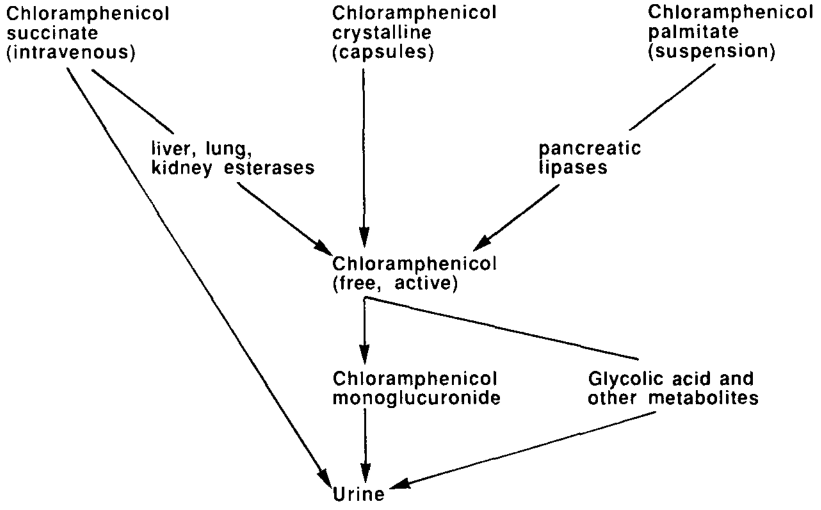
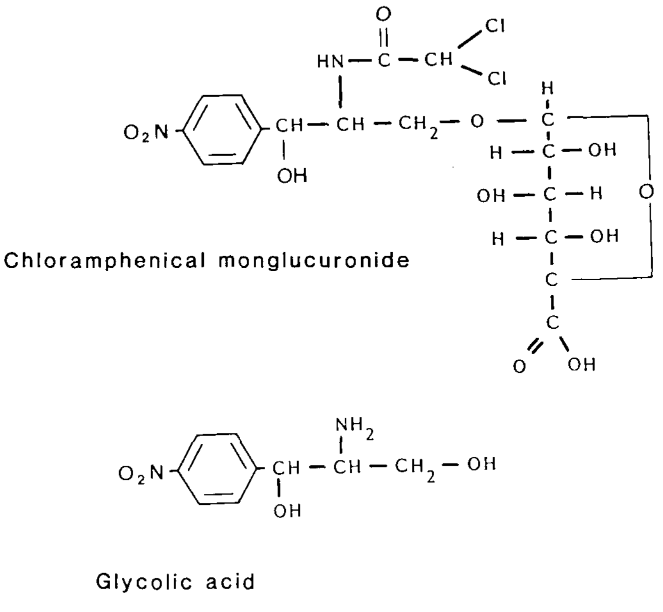

Chloramphenicol succinate (intravenous)
Chloramphenicol crystalline (capsules)
Chloramphenicol palmitate (suspension)
liver, lung, kidney esterases
pancreatic lipases
Chloramphenicol (free, active)
Chloramphenicol monoglucuronide
Glycolic acid and other metabolites
Urine

FIGURE 2. Chloramphenicol metabolic pathways.


O
HN — C — CH
Cl
Cl
O_2N
CH — CH — CH$_2$ — O — C
OH
H
H — C — OH
OH — C — H
H — C — OH
C
C
O
O OH
NH$_2$
CH — CH — CH$_2$ — OH
OH

Chloramphenical monglucuronide

Glycolic acid

FIGURE 3. Chloramphenicol metabolites.

C. METABOLISM

The metabolism of chloramphenicol is depicted in Figure 2. Metabolism of the palmitate and succinate salts has previously been discussed (Section IV.A.2). Following hydrolysis of the succinate or palmitate salts, free chloramphenicol is first bound by a hepatic drug-metabolizing enzyme complex containing cytochrome P450 and subsequently passed through several enzyme systems for conjugation to a water-soluble, inactive monoglucuronide[3] (Figure 3). The glucuronide conjugate is then excreted by active renal tubular secretion.[3,35] The enzyme-metabolizing systems in the newborn are immature.[3] In guinea pigs, glucuronyl transferase enzyme activity is deficient in the fetus and increases during the first few days of life.[62] Decreased glucuronyl transferase activity probably contributes to the slow decline in chloramphenicol serum levels observed in premature and newborn infants compared to that in older infants and children.[41]

Minor chloramphenicol metabolites have been identified and are presumed to be a product of hydrolysis.[35] Trace amounts of aryl amine derivatives have been identified and presumably result from reducing activity of the enteric flora upon chloramphenicol and glucuronide excreted in the bile.[31,63] In the newborn, a glycolic acid metabolite (Figure 3) has also been identified.[3]

Nahata and Powell[31,44,49] have observed substantial variability in nonrenal clearance of chloramphenicol succinate in pediatric patients. These investigators found mean nonrenal clearance rates of 93, 77, and 40% of the mean total clearance in newborn infants, term infants greater than 2 months of age, and children, respectively. In premature and full-term infants as well as older children, the mean nonrenal clearance of chloramphenicol has been found to vary from 72 to 81% of the mean total clearance.[31,44,49]

Some investigators have observed that serum chloramphenicol concentrations did not decline during the dosing interval.[35,39,47,57,61] Although this may be explained by a diminished elimination rate, such an observation would have been made if the elimination rate of chloramphenicol were equal to or less than the rate of hydrolysis of the succinate ester.[35] In most of these cases, serum chloramphenicol succinate concentrations were not determined. However, other investigators have observed measurable concentrations of the intact ester throughout a dosing interval.[35,43,44]

D. EXCRETION

About 90% of a dose of chloramphenicol is excreted as the inactive glucuronide by renal tubular secretion, while 5 to 15% is excreted as the active drug through glomerular filtration.[3,35] In premature and full-term infants as well as older children, the mean renal clearance of chloramphenicol has been reported to be 19 to 28% of the mean total body clearance.[31,44,49] In three neonates, Shankaran and Kauffman[40] found fractional urinary excretion rates of chloramphenicol and the glucuronide ester to be 24 to 55% of the total dose administered. Following intramuscular administration of 25 mg/kg of chloramphenicol succinate, a 12-h urinary excretion of active chloramphenicol was 2.74% in infants 5 d of age; 16.1% in premature/newborn infants from 15 to 30 d of age; 6.8% in infants; and 6.4% in children.[41] The high excretion rate in premature/newborn infants 15 to 30 d of age suggests that renal function has improved beyond its capacity immediately after birth, while urinary excretion in older infants and children approximates that of adults.[41]

Kauffman et al.[4,47] found widely variable (6 to 73%) renal excretion of unchanged chloramphenicol succinate in 63 infants and children 3 d to 16 years old. Nahata and Powell[31,44] and Slaughter et al.[43] found 30 to 40% of chloramphenicol succinate dosages were excreted unchanged by the kidney in pediatric and adult patients. Nahata and Powell[44,49] observed mean renal clearances of 7, 29, and 61% of total clearance of chloramphenicol succinate in newborn infants, full-term infants older than 2 months of age, and children, respectively.

E. HALF-LIFE

The elimination half-life of chloramphenicol has been shown to vary with age. Available data suggest that the half-life is approximately 24 h in newborns 1 to 2 weeks old, 12 h in infants 2 to 4 weeks old, and 4 h in older infants, children, and adults.[44,49,61,64,65]

F. EFFECT OF CONCOMITANT DISEASE STATES

1. Hepatic Dysfunction

Compromised liver function appears to exert a variable effect upon chloramphenicol metabolism.[60] Koup et al.[60] reported that protein binding of chloramphenicol is lower in cirrhotic than in normal adults. Although this difference in protein binding was not necessarily considered clinically significant, cirrhotic patients also exhibited lower total body clearances of chloramphenicol. Prolonged serum half-life and increased levels of free chloramphenicol have been observed in some patients with hepatic insufficiency, including cirrhotics.[63,66] The prolongation of serum half-life has been associated with a reduced rate of metabolism, although the overall metabolism of chloramphenicol appeared to be nearly normal in patients with compromised hepatic function.[62] To avoid excessive serum concentrations which have been associated with an increased risk of chloramphenicol toxicity, it is recommended that chloramphenicol serum concentrations be monitored closely in patients with cirrhosis.

2. Renal Dysfunction

Suhrland and Weisberger[66] observed increased levels of free chloramphenicol in patients with renal insufficiency. Slaughter et al.[43] reported that hydrolysis of chloramphenicol succinate was dependent upon renal function. Patients with impaired renal function have reduced urinary excretion of chloramphenicol succinate.[43] Nahata and Powell[49] examined premature infants and found a relatively greater fraction of chloramphenicol succinate available for hydrolysis which was attributed to reduced renal clearance of chloramphenicol succinate.

Kunin et al.[63] found that the serum half-life of chloramphenicol was similar in normal and anuric patients. However, the serum half-life of chloramphenicol metabolites was markedly increased in patients with severely impaired renal function. Aryl amine derivatives may slowly accumulate in the blood of uremic patients.[63] While there are no recommendations for modifying chloramphenicol doses in patients with compromised renal function, monitoring of serum concentrations is recommended.

3. Shock

Koup et al.[60] observed marked abnormalities and significant differences in chloramphenicol metabolism in three patients in shock. Accumulation of chloramphenicol, increased elimination half-lives, and decreased clearances were associated with deterioration in cardiovascular function. The authors indicated that if shock played a major role in alteration of the pharmacokinetics of chloramphenicol, then one could predict a cycle in which a shock-like state permits elevated chloramphenicol levels which in turn may further impair cardiovascular function.

VII. TOXICITY

A. HEMATOLOGIC

Reports of bone marrow aplasia associated with chloramphenicol appeared soon after its introduction as an antimicrobial agent.[67] Yunis et al.[68] reported that reversible bone marrow suppression resulted from inhibition of mitochondrial protein synthesis. Electron microscopic studies of bone marrow mitochondria in patients receiving chloramphenicol indicated that the drug induced an increase in the density of the mitochondrial matrix. The extent of mitochondrial changes was directly related to concentrations of free chloramphenicol in serum. Yunis et al.[68] indicated that mitochondrial protein synthesis was the only metabolic pathway in mammalian cells that was affected by concentrations of chloramphenicol in the therapeutic range. In a canine model, chloramphenicol inhibited either the synthesis of ferrochelatase or a ferrochelatase binding site on the inner mitochondrial membrane. It was proposed that suppressing ferrochelatase activity and blocking the terminal step of heme synthesis may be responsible for this phenomenon.[69]

Erythropoietic depression is detectable in patients receiving chloramphenicol before abnormalities of peripheral blood elements appear.[66] This depression has been associated with increases in serum iron concentration, increased saturation of iron binding globulin, and delayed plasma iron clearance.[62,70-72] Reticulocytopenia, increase in the myeloid to erythroid cell ratio in the bone marrow, and vacuolization of marrow precursors may occur after 3 to 7 d of drug use.[71-72] A decreased hemoglobin concentration (onset from 5 to 10 d) and mild thrombocytopenia (onset from 10 to 14 d) are common.[71] Neutropenia occurs infrequently and should be considered as an indication for stopping treatment.[71] The incidence of hematologic toxicity is higher in patients with hepatic or renal disease.[66,72] This may be due in part to decreased erythrocyte life span, and inadequate marrow compensatory activity, as well as to higher levels of free chloramphenicol.

A distinction should be made between bone marrow suppression which is a pharmacological effect frequently accompanying chloramphenicol therapy and the occurrence of aplastic anemia.[67] Bone marrow suppression is usually dose related and promptly reversible when the drug is stopped.[67] Chloramphenicol-induced aplastic anemia is rare (incidence of 1 per 25,000 to 40,000), typically within an onset of 2 to 5 weeks or longer after the last dose, and appears unrelated to dose or duration of therapy.[67,71,73] Aplastic anemia is irreversible in most instances and is associated with a mortality rate of 50%.[4,73] Daun et al.[74] reported a case of apparent dose-related marrow suppression which progressed to fatal aplasia following discontinuation of therapy.

Aplastic anemia may be related to the capacity of the compound to inhibit DNA synthesis, perhaps through the nitrobenzene moiety.[69] Conversion into toxic intermediates such as *N*-hydroxyl or nitroso derivatives has been postulated as a possible mechanism for this manifestation of drug toxicity.[69] Chloramphenicol concentrations in excess of 100 μg/ml were required to significantly inhibit DNA synthesis *in vitro* in bone marrow specimens from normal subjects. It should be noted that significant inhibition of DNA synthesis could be demonstrated at chloramphenicol concentrations of 25 to 50 μg/ml in specimens of bone marrow from patients who recovered from chloramphenicol-induced aplastic anemia.[69] Certain characteristics of chloramphenicol-induced aplastic anemia suggest a stem cell lesion, including late clinical onset, involvement of all bone marrow elements, and irreversibility in the majority of cases.[69] Some evidence suggested that aplasia may be associated with a genetically determined defect in the processing of chloramphenicol by bone marrow cells.[69,75] Yunis[69] documented that concentrations of chloramphenicol in the therapeutic range could inhibit DNA synthesis in the bone marrow of two fathers whose offspring developed chloramphenicol-induced aplasia. Nagao and Maurer[75] reported the occurrence of aplastic anemia in identical twins exposed to chloramphenicol, suggesting that genetically determined predisposing factors may be involved. In the second twin, myeloid and erythroid precursor cells decreased first and were the first to reappear during recovery. This observation was consistent with the hypothesis that failure of delivery of differentiated forms from a damaged undifferentiated precursor cell line is the basic mechanism involved in chloramphenicol-induced aplasia.[75]

For some time, aplastic anemia following parenteral administration of chloramphenicol was not reported and was considered not to occur. However, aplasia associated with intravenous administration has been documented and indicates that this side effect is not exclusive to oral therapy.[76] A review of 149 reported chloramphenicol-induced blood dyscrasias revealed that the route of drug administration when this disorder occurred was oral in 83%, parenteral in 14%, and rectal in 3% of cases.

B. GRAY BABY SYNDROME

While the relationship between chloramphenicol and the occurrence of aplastic anemia was of considerable concern shortly following drug introduction, other toxic effects in the newborn were recognized in 1958.[65] The initial recognition of the association of the gray baby syndrome may belong to Lambdin, but it was Sutherland who first reported fatal cardiovascular collapse in infants who received large doses of chloramphenicol.[1] He described two infant deaths which occurred 60 and 72 h after the initiation of intramuscular chloramphenicol in doses of 220 and 226 mg/kg/d. The recommended intramuscular dose of the microcrystalline suspension of chloramphenicol in aqueous vehicle was 100 to 150 mg/kg/d for children weighing 15 kg or less. A third death occurred 10 h after a single oral dose of 125 mg/kg of chloramphenicol palmitate which was inadvertently administered 56 h after beginning oral therapy in a dosage of 50 mg/kg/d. The manufacturer's recommended oral dose of chloramphenicol for children weighing 15 kg or less was 50 to 100 mg/kg/d, although others recommended doses up to 150 mg/kg/d.[1,64] Burns et al.[77] conducted a prospective study of various antibiotic regimens administered to premature infants delivered after prolonged rupture of the fetal membranes. Group 1 received no antibiotics; Group 2 received intramuscular chloramphenicol, 100 to 165 mg/kg/d; Group 3 received procaine penicillin, 150,000 to 600,000 U/d plus streptomycin, 50 mg/kg/d; and Group 4 received chloramphenicol, penicillin, and streptomycin. The mortality rate was 60 and 68% in Groups 2 and 4 receiving chloramphenicol, 19% in the untreated Group 1, and 18% in penicillin- and streptomycin-treated infants (Group 3). The authors concluded that chloramphenicol must have been responsible for the increased mortality. Immature liver function, especially in the glucuronide conjugation system, and decreased renal function were suggested as possible causes for the accumulation of toxic drug levels. Symptoms of the gray baby syndrome include vomiting, anorexia, respiratory distress, abdominal distention, cyanosis, green stools, lethargy, and a striking ashen color.[77] The symptoms began an average of 3.6 d after the initiation of chloramphenicol.[65,77] Improvement occurred within 24 to 36 h after stopping therapy; when fatal, death occurred an average of 2.1 d after the onset of symptoms.[65,77] In a review of the gray baby syndrome, Weiss et al.[64] observed that in most cases, chloramphenicol had been started in the first 48 h of life, and symptoms first appeared after 3 to 4 d with 100 mg/kg/d or more. Progression to death was accelerated in patients who received higher dosages. No characteristic pathological change was found in any organ system, and prompt termination of therapy following early recognition of symptoms often reversed the process and was followed by recovery. Variability in the metabolic disposition of free chloramphenicol in the newborn infant was identified as a likely cause for toxicity. The metabolites of chloramphenicol, including the glycolic acid amide metabolite, appeared to produce little toxicity. Lischner et al.[78] reviewed the unexplained deaths of nine infants who had received relatively large doses of chloramphenicol. These investigators identified symptoms similar to those previously described, with a common factor being administration of chloramphenicol in doses exceeding 113 mg/kg/d for 41 h or longer. Toxic reactions were thought to be related at least in part to impaired glucuronide conjugation and impaired renal excretion leading to blood levels exceeding 100 μg/ml. Evans and Kleiman[79] documented metabolic acidosis as a presenting feature in four critically ill infants with gray baby syndrome. The likely pathogenesis for the acidosis was considered to be chloramphenicol-induced interference with mitochondrial electron transport. At high serum concentrations, chloramphenicol-induced impairment in hepatocyte metabolism probably resulted in interference with its own excretion as well as lactic acid clearance.

Reversible cardiomyopathy has been recognized in association with chloramphenicol toxicity.[80,81] Biancaniello et al.[80] observed deterioration of left ventricular function on the fourth day of treatment concomitant with the presence of toxic chloramphenicol blood concentrations. Fripp et al.[81] observed that acute toxicity may occur through direct interference with tissue respiration in the presence of high chloramphenicol concentrations. Wilkinson and colleagues[82] described hemodynamic and oxygen utilization derangements associated with toxic chloramphenicol serum levels in two young infants with hepatic disease. Both infants received doses of 100 mg/kg/d. Oxygen consumption was depressed in both patients. In one infant, depressed oxygen consumption preceded the development of a low cardiac index and continued when cardiogenic shock developed. This illustrated that cardiac

TABLE 2
Initial Dosage Recommendations for Chloramphenicol

Newborns ≤2 weeks[a]	25 mg/kg in one daily dose
Infants 2—4 weeks[a]	50 mg/kg/d, divided into two equivalent doses administered every 12 h
Older children	75 mg/kg/d, divided into four equivalent doses administered every 6 h

[a] Dosage adjustment may be required based upon the results of serum drug levels obtained after 24 h of therapy and then twice weekly thereafter until steady state is achieved.

depression can be a late manifestation of chloramphenicol toxicity. These findings are consistent with cellular toxicity of chloramphenicol which has been shown to significantly decrease stage three (adenosine diphosphate stimulated) respiration in mitochondria of porcine hearts exposed to toxic drug levels.[81,82]

Gray syndrome has been reported in older children, adolescents, and an infant exposed to large doses in utero and post partum.[79,83,84] Revisions of dosage recommendations, increased awareness, and decreased usage have minimized the incidence of gray baby syndrome. The syndrome is occasionally seen as a result of dosing and administration errors.

Charcoal hemoperfusion and exchange transfusion have been utilized to lower toxic blood chloramphenicol concentrations.[82,85-88] Hemodialysis and peritoneal dialysis do not remove significant quantities of chloramphenicol.[35] Freundlich et al.[88] reported that two sequential single blood volume exchange transfusions resulted in a 15% decrease in serum chloramphenicol levels in an infant with gray baby syndrome, and 4 h later, serum chloramphenicol levels had increased to preexchange values. Charcoal hemoperfusion was initiated, resulting in a 60% decrease in levels after 140 min and an additional 18% decrease at 260 min. Kessler et al.[86] reported that eight to ten two-volume exchange transfusions during a 43-h period lowered serum chloramphenicol levels from 135 to less than 10 μg/ml in an infant who inadvertently received a tenfold drug overdose. Stevens et al.[87] reported that clearance of chloramphenicol was impaired in a 5-week-old infant with toxic drug levels which also were associated with a tenfold overdose. A single-volume exchange transfusion was begun at 32 h and double-volume exchanges were begun at 38 and 42 h. Only 14% of the administered dose were removed from the blood, which may be related to the large volume of distribution of chloramphenicol. Charcoal hemoperfusion may be the procedure of choice to decrease chloramphenicol toxic serum levels in the presence of clinical or laboratory abnormalities, especially in the presence of hepatic dysfunction. Large-volume exchange transfusions may be effective if charcoal hemoperfusion is not available.

VIII. DOSING

Dosage recommendations for chloramphenicol are listed in Table 2. Dosages are not influenced by the route of administration (oral vs. intravenous). McCracken and Nelson[89] recommended that a single, 25-mg/kg daily dosage should be administered to infants 2 to 4 weeks of age who weigh 2 kg or less. Dosage recommendations are suggested as initial guidelines only and serum concentrations should be routinely monitored, especially in newborn patients with hepatic dysfunction and in the presence of severe renal disease.

The effect of intravenous flow rate and injection site on pharmacokinetics of chloramphenicol succinate must be considered. Nahata et al.[90] found that flashball injections resulted in significantly higher chloramphenicol succinate and chloramphenicol concentrations than Buretrol® injections. The mean time to peak serum concentration was also shorter with the flashball injection. The actual times required for 95% delivery of chloramphenicol succinate from three injection sites (Buretrol® Y-site, flashball) were two- to fourfold longer than the infusion times predicted from intravenous flow rates. Lack of consideration of these factors may result in inappropriate interpretation of chloramphenicol serum levels.

TABLE 3
Drugs which May Interact with Chloramphenicol

Barbiturates
Dicumarol
Phenytoin
Rifampin

The anticoagulant activity of dicumarol may be enhanced by the concurrent administration of chloramphenicol[91] (Table 3). Although no documentation exists, a similar interaction may occur with warfarin. Anticoagulant metabolism is inhibited because chloramphenicol inhibits the hepatic microsomal enzyme activity. Coadministration of chloramphenicol with barbiturates may result in decreased chloramphenicol serum levels in infants and children and potential enhancement of barbiturate effect due to decreased barbiturate clearance.[91,92] The decrease in chloramphenicol levels is likely the result of induction of hepatic metabolizing enzymes by barbiturates. It is postulated that chloramphenicol may also inhibit barbiturate metabolism.[91] Concomitant administration of chloramphenicol and phenytoin may result in altered pharmacology of both drugs.[93] The serum concentrations of each should be monitored to identify the need for dosage adjustments. Rifampin, a known inducer of hepatic enzymes, may also significantly decrease serum concentrations of chloramphenicol.[94]

IX. THERAPEUTIC MONITORING

Therapeutic monitoring of serum chloramphenicol concentrations in infants and children is essential. It is important that the assay utilized distinguish active chloramphenicol from its inactive and presumably nontoxic precursor (chloramphenicol succinate) or its inactive and presumably nontoxic metabolites (chloramphenicol glucuronide and the glycolic acid analog).[65] Peak serum concentrations should be drawn 1.5 to 3 h after oral administration of chloramphenicol palmitate and 0.5 to 1.5 h after a 30-min intravenous infusion of chloramphenicol succinate.[30] Serum concentrations should be drawn when a steady state is reached, which should occur within 24 h after initiation of therapy. In newborns, who have extended half-lives, a minimum of 2 to 3 d of therapy may be required to attain steady state.[31]

Patients who receive chloramphenicol should have reticulocyte, white blood cell, platelet, and hemoglobin determinations at the outset of therapy.[71] These measurements should be repeated after 1 week and approximately every 3 d thereafter if treatment is continued longer than 1 week.[71]

X. CURRENT INDICATIONS FOR CLINICAL USE

The renaissance in the use of chloramphenicol has begun to subside with the availability of less toxic, effective alternatives.[95] Currently, chloramphenicol is a drug of choice, along with tetracycline, in the treatment of Q fever, rickettsial infections including Rocky Mountain spotted fever, and endemic typhus.[96] Chloramphenicol is still widely used as empiric therapy, along with ampicillin, for the treatment of suspected sepsis and meningitis in children beyond the newborn period, but younger than 6 years of age, or in other clinical situations in which invasive and life-threatening infection with *H. influenzae* is suspected. Chloramphenicol is still the standard of therapy for typhoid fever and occasionally for other instances of severe infection with *Salmonella* sp. which require antimicrobial treatment. It enjoys some use for treatment of anaerobic infections, especially those caused by *B. fragilis*, but the availability for other effective agents has decreased its role for these infections. Chloramphenicol is used in patients with allergic reactions to beta-lactam antibiotics or in cases in which resistance to alternative agents is known or suspected.

XI. SUMMARY

Chloramphenicol is a unique antibiotic with variable pharmacokinetics and limited use secondary to toxicity. The increased knowledge of pharmacokinetics has assisted in maximizing the efficacy of chloramphenicol while minimizing the incidence of toxicity. Additional clarification of its optimal place for the treatment of meningitis and anaerobic infections awaits additional trials. The lingering concerns about its propensity to cause fatal, albeit rare, aplastic anemia appropriately limit the use of this agent when other well-tested, effective, and safe alternatives are available.

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Chapter 9

DEVELOPMENTAL PHARMACOLOGY OF AMINOGLYCOSIDES AND VANCOMYCIN

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TABLE OF CONTENTS

I. Introduction 174

II. Aminoglycosides 174
  A. Clinical Pharmacology 174
  B. Adverse Effects 175
    1. Nephrotoxicity 175
    2. Experimental Approach for Comparison of Aminoglycoside Nephrotoxicity 176
    3. Ototoxicity 177

III. Vancomycin 178
  A. Adverse Effects 179
    1. Nephrotoxicity 179
    2. Ototoxicity 180
    3. Hypersensitivity Reactions 180
    4. Miscellaneous Adverse Effects 181

IV. Summary 181

Acknowledgment 183

References 184

I. INTRODUCTION

Aminoglycosides are the most widely used antibiotics in the neonatal intensive care unit[1] for the treatment of Gram-negative septicemia, meningitis, and necrotizing enterocolitis. Later in infancy and childhood, they are used to treat the bacteremia-septicemia of the immunosuppressed and Gram-negative infections complicating cystic fibrosis. The use of vancomycin as an antistaphylococcal agent has emerged recently parallel to the development of staphylococcal resistance against the penicillins.[2]

Despite their different range of antimicrobial activity, the aminoglycosides and vancomycin share some similar adverse effects. Moreover, recent work has documented their synergistic capability to produce renal adverse effects. This chapter will focus on the developmental aspects of disposition and toxicology of aminoglycosides and vancomycin in an attempt to delineate their rational use in the pediatric age group.

II. AMINOGLYCOSIDES

A. CLINICAL PHARMACOLOGY

Aminoglycosides are administered in the pediatric group intravenously or intramuscularly. Topical use is available for ophthalmic and optic inflamations, and direct injection into the vitreous humor is available for endophthalmitis. For skin infections with the appropriate organism, an ointment is available, and in cases of Gram-negative ventriculitis, a direct injection through a reservoir is often used.[3,4] Although skin and intestinal absorption of hydrophilic compounds such as aminoglycosides is believed to be low, the newborn infant shows substantially higher permeability than adults. There are cases where serum concentrations in the high therapeutic range have been reported following 15 mg/kg of oral gentamicin.[5] Deafness in a preterm baby has been described following topical antibiotic spray containing neomycin. Transplacental passage of aminoglycosides is well documented, and there are several reports of ototoxicity following maternal use of streptomycin and kanamycin; however, similar reports are not available for any of the newer, currently used aminoglycosides.[7]

All aminoglycosides have low protein binding (<20%), and their minimal tissue distribution is determined mainly by their polarity. Low concentrations can be found in most tissues, and this corresponds to an apparent volume of distribution in the range of the extracellular fluid. On the other hand, the two target organs of aminoglycoside toxicity have high concentrations of these drugs: both the renal cortex and perilymph and endolymph of the internal ear concentrate aminoglycosides.

Undoubtedly, the most important pharmacokinetic determinant of aminoglycoside toxicity during development is the GFR-dependent excretion of these compounds. Being only slightly bound to plasma proteins, the filtration of aminoglycosides closely parallels that of inulin or creatinine.[8] Subsequently, they undergo some tubular reabsorption followed by their possible release into the systemic circulation, accounting for the prolonged terminal half-life.[9] We found good correlation between gentamicin plasma clearance or $t_{1/2}$ and creatinine clearance in newborn infants.[8]

During steady state, the dose required to achieve a target serum concentration depends on the clearance of the drug according to the equation:

$$\text{Serum concentration} = \frac{\text{dose (mg/Kg/hr)}}{\text{clearance}}$$

Dose interval (τ) depends on the elimination $t_{1/2}$ of the drug:

$$\tau = 1.44 \times t_{1/2} \ln \frac{C_{max}}{C_{min}}$$

where C_{max} and C_{min} are the desired peak and trough concentrations. Because both clearance and $t_{1/2}$ of aminoglycosides closely correlate with GFR,[8] which is dependent on maturation of the glomerular apparatus, guidelines for rational dosing should consider the age of the neonate. Our analysis reveals that postconceptional age (the summation of gestational and postnatal age) is the most accurate marker of maturation of aminoglycoside disposition. Unlike clearance rate and $t_{1/2}$, the distribution volume of aminoglycosides standardized for body weight, does not appear to be age dependent. Within the group of very small preterm infants, it appears that infants less than 1 kg of body weight are likely to need significantly less gentamicin per kilogram of body weight when compared to those >1 kg.[8]

Because of the large variability in the pharmacokinetics of aminoglycosides in newborn infants, the age-dependent guidelines can only serve as a general frame for dosing; therapeutic drug monitoring will always be needed for the individual case.[10] Specifically, it should be remembered that infants receiving aminoglycosides are often in a critical state due to sepsis, enterocolitis, etc. It is possible that GFR decreases and loses its association with age. Similarly, drugs which are known to decrease GFR, such as indomithacin and cyclosporine, may cause accumulation of aminoglycosides if the dose was not decreased proportionally to the decrease in GFR. Recently we showed that indomethacin, given to newborn infants for medical closure of their ductus arteriosus, causes accumulation of gentamicin and amikacin[11] (Figure 1).

Finally, aminoglycosides themselves, by impairing GFR, may cause a negative feedback of their own excretion. Typically in such cases, there is a gradual increase in plasma creatinine and serum aminoglycoside concentrations in the presence of unchanged doses.

B. ADVERSE EFFECTS

Typical of drugs with large clinical use, a long list of adverse reactions have been associated with aminoglycosides. While hypersensitivity reactions, bone marrow suppression, bleeding diathesis, and neuritis are not dose dependent, neuromuscular blockade, nephrotoxicity, and ototoxicity depend on the dose administered to the child.

1. Nephrotoxicity

Following glomerular filtration, some of the load of the aminoglycoside is taken up by the proximal tubular cell and concentrated mainly in the lysosomes, where they appear to displace calcium from neutral lipids.[12,13] The sequestration of aminoglycosides by the lysosome is temporally related to morphological changes in the tubular cell, such as the appearance of myeloid bodies and cytosegrosomes and the accumulation of electron dense polar lipids (Plate 3*). It has been postulated that by binding to lipids, the environment essential for enzyme function is altered. Although the chain of events leading to proximal tubular cell death is yet unclear, the damage to the proximal convoluted tubules is beyond doubt.

Nephrotoxicity of aminoglycosides is enhanced by sodium or potassium depletion, dehydration, and by several commonly coadministered drugs, including amphotericin B, cephalothin and cephaloridine, cisplatinum, loop diuretics (furosemide and ethacrynic acid), vancomycin.[3] On the other hand, amiloride appears to reduce the nephrotoxicity of aminoglycosides, probably by reducing antibiotic uptake by the renal tubular cell. Although the exact therapeutic window of aminoglycoside serum concentration is difficult to predict, it is generally accepted that high peak (above 8 to 10 μg/ml for gentamicin) and trough concentrations (above 2 to 3 μg/ml) are associated with a higher rate of nephrotoxicity.[14]

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* Plate 3 appears following page 182.

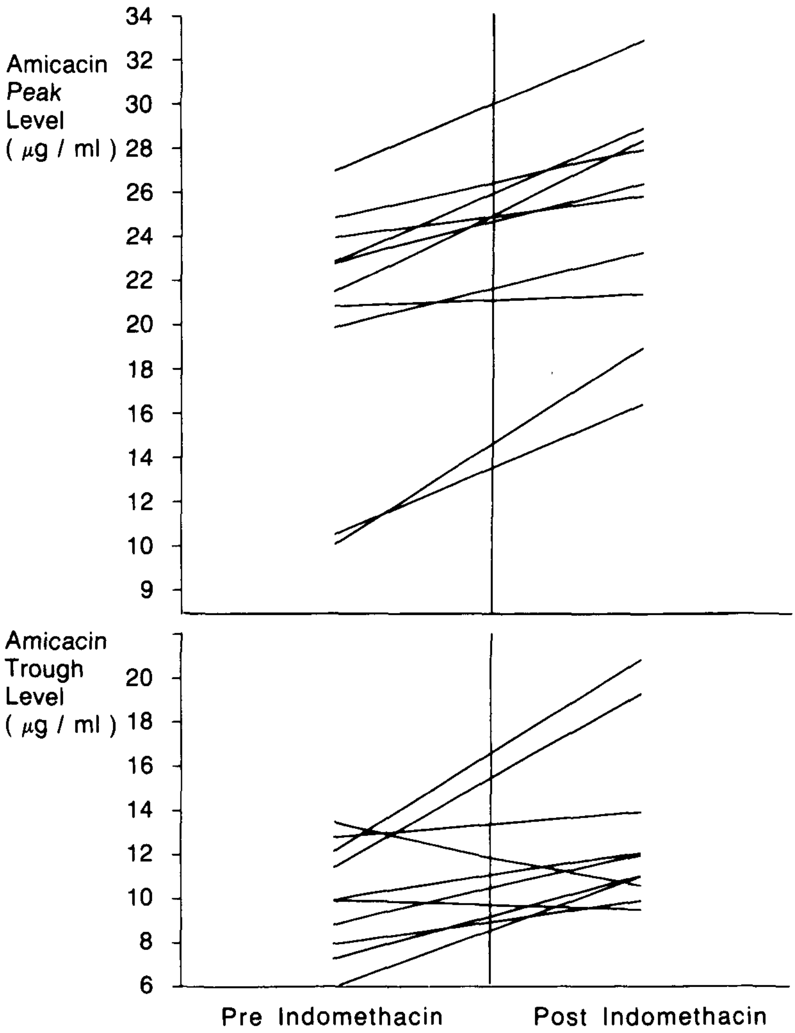


FIGURE 1. Increase in steady-state concentrations of amikacin in rats receiving concomitantly indomethacin.

2. Experimental Approach for Comparison of Aminoglycoside Nephrotoxicity

Knowing that every aminoglycoside is potentially capable of producing renal damage, it is logical to try to identify the relative toxic potencies of aminoglycosides in order to include this information in the rational choice of drug. Because therapeutic drug monitoring is part and parcel of any contemporary use of these agents, it is inconceivable that overt toxicity will occur in high frequencies with any of the currently used aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin). Moreover, changes in markers such as plasma creatinine or creatinine clearance are likely to occur only late in the development of aminoglycoside toxicity.[3]

Recently, cellular markers which appear in the urine in cases of tubular damage have been utilized to assess renal toxicity of these drugs. The lysosomal enzyme *N*-acetyl-β-glucosaminidase (NAG) has been shown to be excreted after proximal tubular damage. Similarly, β_2-microglobulin, a low-molecular-weight protein which is filtered at the glomerulus and reabsorbed by the proximal tubule cell, appears in the urine following tubular damage. Unlike changes in creatinine, which reflect a gross renal damage, the appearance of NAG and β_2-microglobulin in the urine occurs early in the course of aminoglycoside nephrotoxicity.[28]

In 1984, Rajchgot and colleagues[15] compared the urinary secretion of NAG and β_2-microglobulin in preterm infants during presumed sepsis and showed that the NAG excretion rate was significantly higher in gentamicin-treated patients (138 ± 10 U/min, mean ± SE) than in amikacin-treated patients (85 ± 7 μ/min). In fact, the enzymuria associated with amikacin was not higher than in the control group which received chloramphenicol. Excretion of β_2-microglobulin did not differ among the three groups. These researchers did not find significant differences in mean peak or trough gentamicin serum concentrations between patients exhibiting very high or very low excretion rate of NAG.[15]

Several researchers have suggested that newborn infants are less susceptible to aminoglycoside nephrotoxicity than older children and adults; however, it is impossible to verify this assumption with the limited existing human data. In order to test this hypothesis, we recently studied the age-dependent effects of amikacin and gentamicin on renal function in Wistar rats. Newborn, 1-week-old, and adult rats received subcutaneously either gentamicin (5, 10, or 20 mg/kg/d) or amikacin (5, 20, or 40 mg/kg/d) for 7 d. In adults and 1-week-old rats, serum creatinine did not change with any of the dose regimens tested, whereas in 2-week-old rats, there was a significant increase caused by the highest dose of gentamicin (Table 1). The highest dose of gentamicin (40 mg/kg/d) was associated with a significant decrease in urine creatinine concentration in adult and 2-week-old rats, whereas 20 mg/kg/d adversely affected only the 2-week-old rats. 1-week-old rats did not show significant changes in their urinary creatinine by any of the dose regimens used (Table 2).

Urinary excretion of NAG increased with both drugs at all doses tested; however, in most cases, amikacin produced a smaller increase (Table 3). Only β_2-microglobulin showed a different pattern of excretion in the 1-week-old rat when compared to 2-week-old and adult rats. The concentration of this protein in the urine of 1-week-old rats did not increase, whereas it did rise significantly in the other two age groups (Table 4). Similar to its effect on NAG, amikacin produced a smaller increase of β_2-microglobulin excretion when compared to gentamicin.

These results are essentially similar to those reported by Rajchgot et al.[15] in newborn infants, with a greater effect of gentamicin when compared to amikacin on NAG and no effect on β_2-microglobulin. Using the lysosomal fraction from kidney cortex homogenate, we compared the effect of the different dosages of gentamicin and amikacin on sphingomyelinase (SM) activity. Amikacin did not inhibit the activity of this enzyme at any age and at any dose used, whereas gentamicin adversely affected the enzyme in a dose- and age-dependent fashion. In adult rats, both high and intermediate doses affected the enzyme; in 2-week-old rats, only the highest dose produced an effect, whereas in 1-week-old rats, no effect was detected (Table 5).

The relative resistance of the newborn to the tubular insult induced by aminoglycosides may be explained by the impaired ability of the immature tubular apparatus to reabsorb the drugs. In our experiments, newborn rats had higher concentrations of gentamicin in their blood and lower renal tissue concentrations. With age, the ratio of renal to blood gentamicin concentrations increased (Table 6).

3. Ototoxicity

Because of the wide use of streptomycin against tuberculosis, the ototoxic potential of aminoglycosides became apparent quite early in their clinical use. The withdrawal of dihydrostreptomycin from treatment of tuberculosis and of systemic neomycin use was based on their high rate of ototoxicity. Animal studies have shown that aminoglycosides damage hair cells in the organ of Corti. It was postulated that, similar to the renal tubular cell, aminoglycosides are bound to a lipid receptor.[3]

TABLE 1
Age-Dependent Effect of Injection of Gentamicin and Amikacin for 1 Week on Serum Creatinine in Rats

Dosage (mg/kg/d)	Gentamicin (n = 6)	Amikacin (n = 6)
10		
1 week	0.31 ± 0.08	0.38 ± 0.05
2 weeks	0.38 ± 0.05	0.30 ± 0.02
Adult	0.32 ± 0.02	<0.30
20		
1 week	0.45 ± 0.15	
2 weeks	0.54 ± 0.11	
Adult	0.31 ± 0.017	
40		
1 week	0.66 ± 0.15	<0.30
2 weeks	1.53 ± 0.27[a]	<0.30
Adult	0.63 ± 0.20	<0.30
80		
1 week		0.35 ± 0.034
2 weeks		0.78 ± 0.21
Adult		0.417 ± 0.040

Note: Newborn, 1-week-old, and adult rats were treated for 7 d. Serum creatinine is expressed as milligrams per deciliter plus or minus standard error of measurement (mg/dl ± SEM): control for 1 week is 0.30 ± 0.04; for 2 weeks is 0.47 ± 0.07[a]; for adult is 0.36 ± 0.04.

[a] $p < 0.02$.

Different studies in preterm infants given different aminoglycosides have reported sensorineural hearing loss in 2 to 7% of the patients.[16,17] Comparison of amikacin to netilmicin ototoxicity did not reveal significant differences, with 1:50 and 1:49, respectively. Most importantly, the control group also had a single similar case.[16] This first prospective, controlled, longitudinal study concluded that the risk of developing clinically significant hearing impairment from a 3- to 7-day course of aminoglycoside therapy is small. However, this conclusion may be too broad, as both amikacin and netilmicin are less ototoxic than the commonly used gentamicin and tobramycin.[3] In older children receiving aminoglycosides, the occurrence rate of ototoxicity is probably smaller. Children with cystic fibrosis who are likely to receive aminoglycosides over a long period of time may be theoretically protected from ototoxicity by the higher clearance rate of the drug and the resultant lower serum concentrations.

III. VANCOMYCIN

During the last few years, vancomycin has been enjoying a renaissance in pediatric use due to the emergence of *Staphylococcus* resistant to other drugs. Its use is confined mainly to the intravenous route, although the minimal oral absorption may be clinically meaningful in patients with renal failure.[18] Similar to the aminoglycosides, the body load of vancomycin is eliminated almost entirely as the unchanged drug via the kidneys. We have recently studied the maturation of vancomycin clearance and $t_{1/2}$ in preterm infants[19] and documented excellent correlation between these values and postconceptional age or body weight (Figure 2). Based on these values, we proposed dose recommendations which are changed with increasing age

TABLE 2
Age-Dependent Effect of Injection of Gentamicin and Amikacin for 1 Week on Urine Creatinine in Rats

Dosage (mg/kg/d)	Gentamicin (n = 6)	Amikacin (n = 6)
10		
1 week	8.60 ± 0.95	9.01 ± 1.18
2 weeks	25.86 ± 4.28	26.01 ± 3.53
Adult	89.40 ± 15.06	95.33 ± 14.38
20		
1 week	9.41 ± 0.78	
2 weeks	16.45 ± 1.49^a	
Adult	66.66 ± 20.07	
40		
1 week	9.52 ± 0.45	9.90 ± 1.70
2 weeks	11.40 ± 1.31^a	28.13 ± 3.68
Adult	42.50 ± 5.78^b	109.00 ± 15.77
80		
1 week		10.5 ± 1.18
2 weeks		20.61 ± 1.23
Adult		106.80 ± 26.35

Note: Newborn, 1-week-old, and adult rats were treated for 7 d. Urine creatinine is expressed as milligrams per deciliter plus or minus standard error of measurement (mg/dl ± SEM): control for 1 week is 8.35 ± 2.14; for 2 weeks is 25.07 ± 1.66^a; for adult is 105.20 ± 11.41^b.

[a] $p < 0.05$.
[b] $p < 0.02$.

or weight (Table 7). A prospective verification of these guidelines[20] could significantly improve the percentage of levels within the accepted therapeutic range (peak, 25 to 40 μg/ml; trough, <10 μg/ml). Because of the potential toxicity associated with a rapid infusion (see below), the intravenous dose should be delivered over at least 30 to 60 min.

A. ADVERSE EFFECTS

1. Nephrotoxicity

It appears that with increased purity of vancomycin over the last two decades, the rate of renal damage has significantly decreased. In a recent series summarizing the experience from 1974 to 1981, Farber and Moellering[21] have found a 5% rate of renal damage evidenced by increased serum creatinine. All patients with renal damage had high vancomycin concentrations (peaks, 49 to 76 μg/ml; trough, 39 to 65 μg/ml). In children, vancomycin-induced nephrotoxicity was reported in 2 of 19 patients by Dean et al.[22]

Several studies have documented synergistic nephrotoxicity when vancomycin and aminoglycosides were combined.[21,23] When both aminoglycosides and vancomycin are administered, the rate of nephrotoxicity may increase to 35%.[21] Consequently, careful monitoring of both drugs levels should be performed in such situations parallel to repeated evaluation of renal function. In the available retrospective studies, it appears that in most cases of synergistic nephrotoxicity, concentrations of vancomycin were not excessive.

TABLE 3
Age-Dependent Effect of Injection of Gentamicin and Amikacin for 1 Week on Urinary *N*-Acetyl-β-glucosaminidase (NAG)

Dosage (mg/kg/d)	Gentamicin (n = 6)	Amikacin (n = 6)
10		
1 week	5992 ± 578	7516 ± 1074
2 weeks	4054 ± 477	3439 ± 364
Adult	2256 ± 290	2198 ± 171
20		
1 week	6418 ± 800	
2 weeks	3735 ± 408[a]	
Adult	5301 ± 549[b]	
40		
1 week	9029 ± 1013	7443 ± 828
2 weeks	6854 ± 762[c]	3838 ± 957
Adult	5600 ± 838[b]	4103 ± 90
80		
1 week		5974 ± 673
2 weeks		4092 ± 767
Adult		5694 ± 429[b]

Note: Newborn, 1-week-old, and adult rats were treated for 7 d. Urinary NAG is expressed as micromoles per milligram of creatinine plus or minus standard error of measurement (μmol/mg creat ± SEM): control for 1 week is 4056 ± 635; for 2 weeks is 2380 ± 46[a,c]; for adult is 2270 ± 526[b]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.005$.

2. Ototoxicity

Unlike the aminoglycosides, present data are not conclusive with respect to the potential ototoxic effects of vancomycin. Similar to negative animal studies,[24,25] recent retrospective and prospective analyses in man have failed to show evidence of ototoxicity. In some instances, aminoglycosides were also used and currently most positive evidence relies on case reports.[2] Recently, Brummett[26] reviewed the available evidence for vancomycin ototoxicity and concluded that the existing cases may not be attributed to this drug.

3. Hypersensitivity Reactions

Typically, during or soon after a relatively rapid infusion of vancomycin, there is appearance of flushing, macular or maculopapular rash of neck, face, trunk and extremities, hypotension and bradycardia.[2] This reaction is explained by a systemic release of histamine. Several cases of severe shock and even sudden death have recently been described in children and newborn infants.[27] We have recently encountered severe hypotension in an immunosuppressed child during his first dose which was infused over 20 min. Serum concentrations of the drug were, as expected for a first dose, in the low therapeutic range. Because continuation of the drug was indicated by the sensitivity of the pathogen, vancomycin was repeated, this time over 45 min after pretreating the child with an antihistamine; no adverse effect was experienced.

Although the incidence of this serious reaction has not been estimated, we have not encountered such cases in more than 50 newborn infants included in our recent pharma-

TABLE 4
Age-Dependent Effect of Injection of Gentamicin and Amikacin for 1 Week on Urinary β_2-Microglobulin

Dosage (mg/kg/d)	Gentamicin (n = 6)	Amikacin (n = 6)
10		
1 week	11.20 ± 1.06	18.50 ± 2.46
2 weeks	6.20 ± 1.15	10.00 ± 2.70
Adult	5.33 ± 1.20	3.33 ± 1.20
20		
1 week	17.00 ± 3.40	
2 weeks	8.33 ± 1.11	
Adult	3.60 ± 0.74	
40		
1 week	18.20 ± 2.46	15.20 ± 2.80
2 weeks	55.50 ± 3.25[a]	5.00 ± 1.50
Adult	30.33 ± 3.08[a]	5.40 ± 0.70
80		
1 week		19.00 ± 3.21
2 weeks		44.20 ± 4.57[a]
Adult		14.50 ± 1.04[a]

Note: Newborn, 1-week-old, and adult rats were treated for 7 d. Urinary β_2-microglobulin is expressed as nanograms per milligram of creatinine plus or minus standard error of measurement (ng/mg creat ± SEM): control for 1 week is 14.20 ± 2.92; for 2 weeks is 10.75 ± 1.25[a]; for adult is 6.00 ± 1.04[a].

[a] $p < 0.01$.

cokinetic studies.[19,20] It is important to remember that this manifestation is not an allergic reaction and can be prevented in subsequent doses by decreasing the rate of infusion and by diluting the solution to less than 10 mg/ml.

4. Miscellaneous Adverse Effects

Phlebitis has been described in up to 13% of cases with vancomycin administration. Nausea, anaphylaxis, chills, fever, hematologic alterations, such as neutropenia or eosinophilia, have been rarely reported.

IV. SUMMARY

Aminoglycosides and vancomycin are drugs with a low therapeutic index, and even recommended doses may be associated with serious adverse affects. Because of large interpatient variability in pharmacokinetics, individualization of therapy should be based on repeated monitoring of serum concentrations. More studies are needed to elucidate the molecular basis of aminoglycosides and vancomycin toxicology. Also, it will be important to correlate the existence and degree of enzymuria, β-microglobuluria, and other putative markers of renal damage with the long-term effect of these drugs on renal function. Because most preterm infants receive aminoglycosides and many of them are likely to be exposed as well to vancomycin, a prospective, comparative assessment of rates of adverse effects and of factors likely to augment them should continue.

TABLE 5
Age-Dependent Sphingomyelinase (SM) Activity in Renal Cortex Homogenate Following Injection of Gentamicin and Amikacin for 1 Week

Dosage (mg/kg/d)	Gentamicin (n = 6)	Amikacin (n = 6)
10		
1 week	88.83 ± 2.61	107.16 ± 4.45
2 weeks	90.53 ± 6.05	101.66 ± 1.94
Adult	85.33 ± 4.51	104.5 ± 5.30
20		
1 week	85.66 ± 5.49	
2 weeks	76.33 ± 3.11	
Adult	64.88 ± 2.70	
40		
1 week	75.33 ± 4.65	100.16 ± 3.70
2 weeks	74.10 ± 2.93	98.91 ± 5.38
Adult	56.16 ± 2.72	107.66 ± 8.44
80		
1 week		97.16 ± 9.04
2 weeks		95.83 ± 3.07
Adult		87.06 ± 3.91

Note: Newborn, 1-week-old, and adult rats were treated for 7 d. SM activity in kidney cortex homogenate is expressed as percent of the control plus or minus standard error of measurement: control for 1 week is 6.99 ± 0.88 (100 ± 12.8%); for 2 weeks is 5.90 ± 0.85 (100 ± 14.4%); for adult is 6.06 ± 0.77 (100 ± 18.6%).

TABLE 6
Age-Dependent Ratio of Renal to Blood Concentration of Gentamicin in Rats

Dosage (mg/kg/d)	Gentamicin serum concentrations (μg/ml) (n = 6)	Gentamicin tissue concentrations (μg/mg protein) (n = 2)	Tissue serum concentrations ratio
10			
1 week	0.83 ± 0.24	0.83	1
2 weeks	0.63 ± 0.08	1.34	2.13
Adult	0.15 ± 0.08	1.02	6.8
20			
1 week	1.10 ± 0.19	1.12	1
2 weeks	1.37 ± 0.14	1.41	1.03
Adult	0.53 ± 0.18	1.8	3.4
40			
1 week	2.87 ± 1.02	1.43	0.5
2 weeks	8.4 ± 3.06	4.2	0.5
Adult	0.18 ± 0.07	Not available	Not available

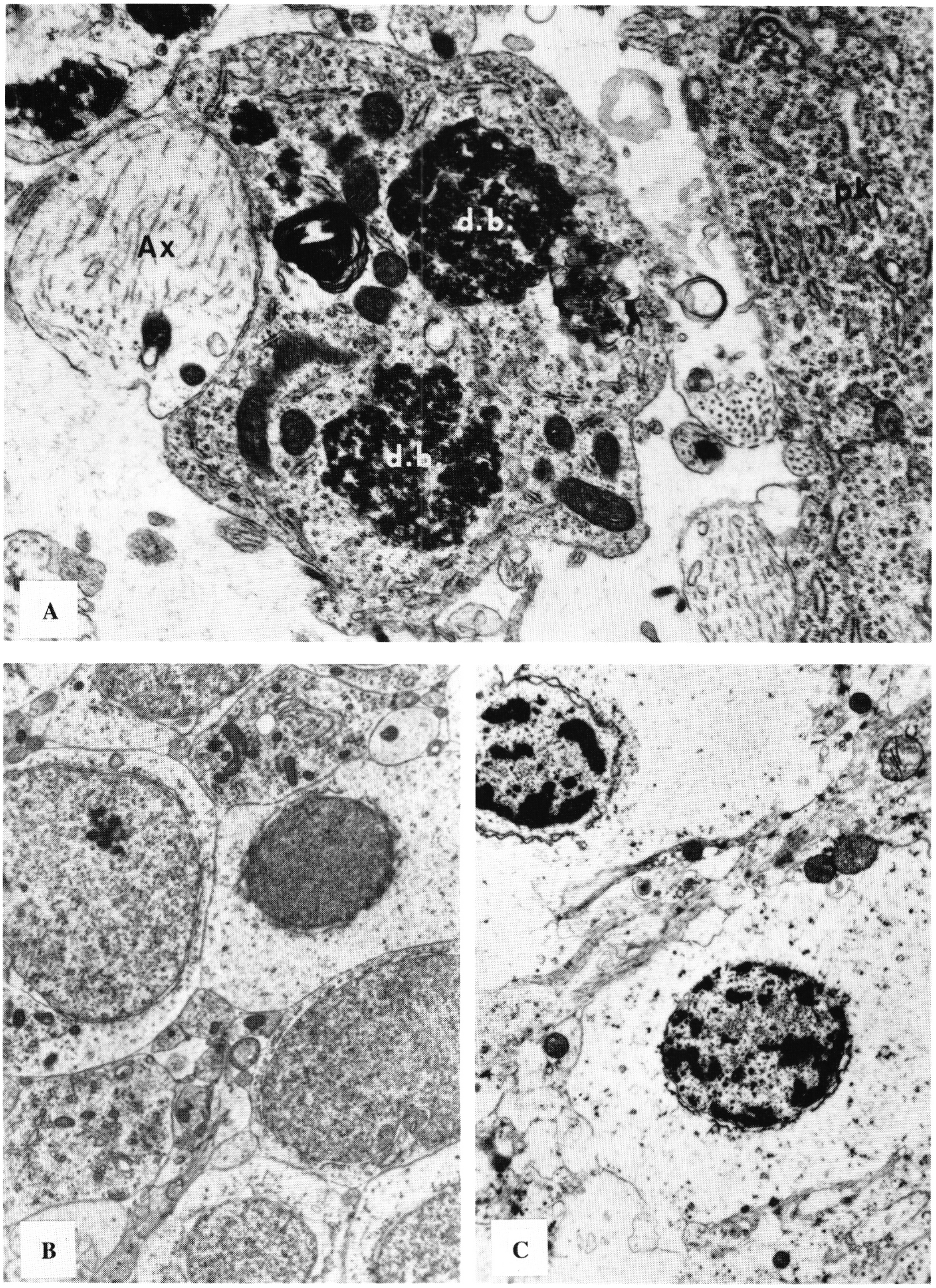
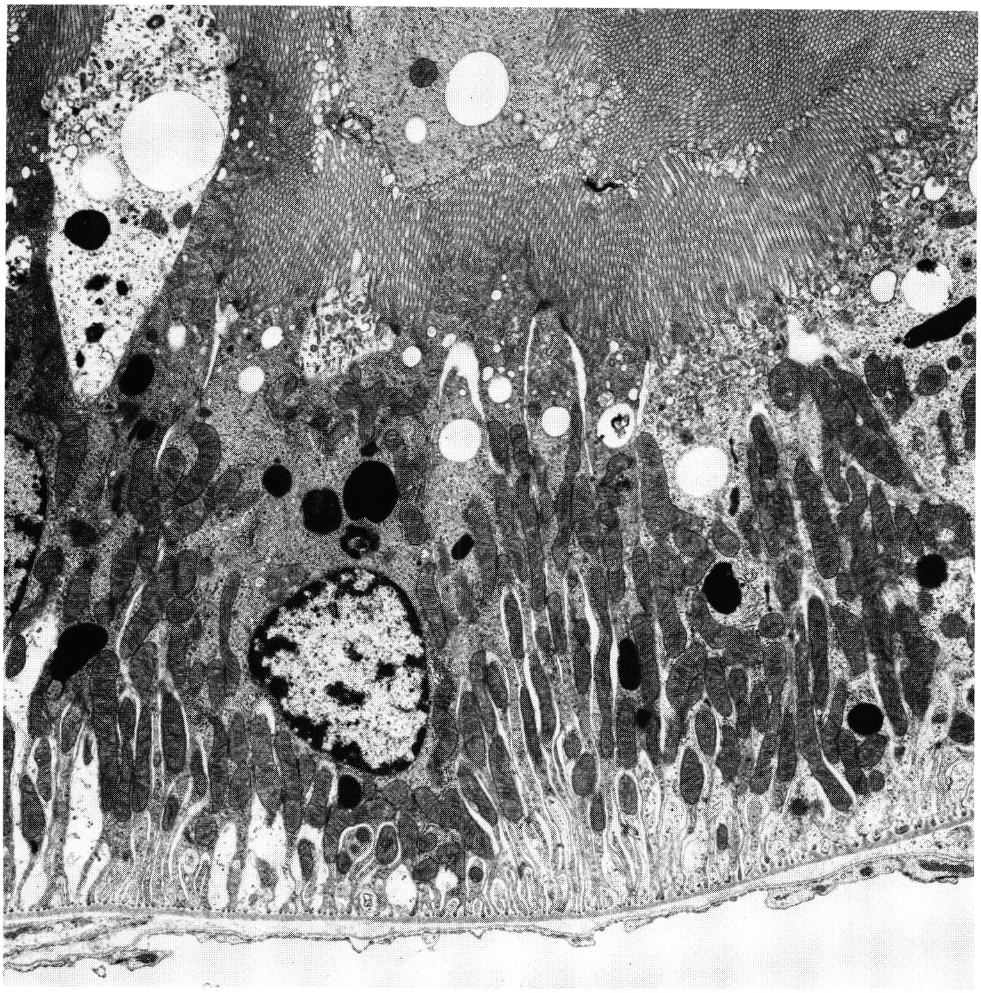


PLATE 2. (A) Electron micrograph from the striatum 48 h after the injection of cisplatin. Note the large dense bodies (d.b.) in a dendrite. Ax: axon; p.k.: perikarion. (Magnification × 17,000.) (B) Degenerating zone in the striatum 4 d after the injection of cisplatin. Most neurons show cytoplasmic lysis and dense bodies as well, as most cytoplasmic organelles have disappeared. (Magnification × 6400.) (C) Degenerating zone in the striatum 4 d after the injection. Note nuclear pyknosis in addition to cytoplasmic lysis. (Magnification × 6400.)



A

PLATE 3. Appearance of electron-dense polar lipids in rat tubular cells exposed to gentamicin. (A) Control; (B) treated.

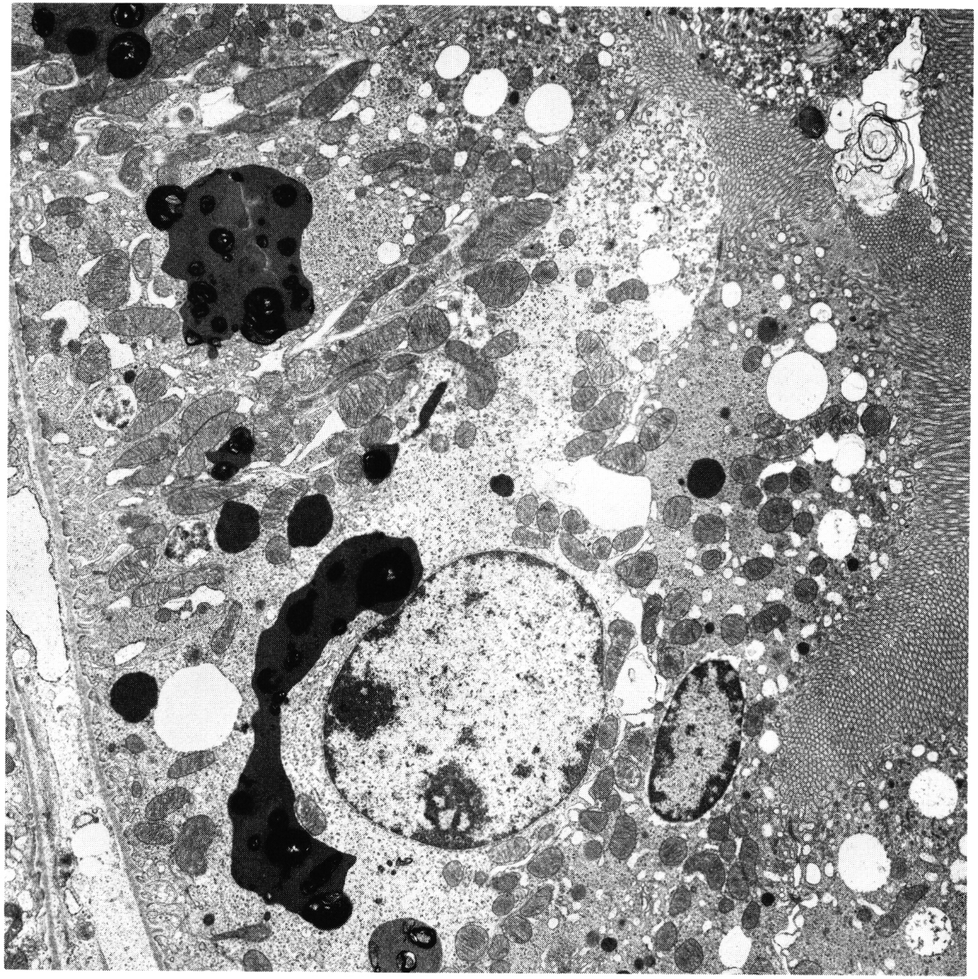


PLATE 3B

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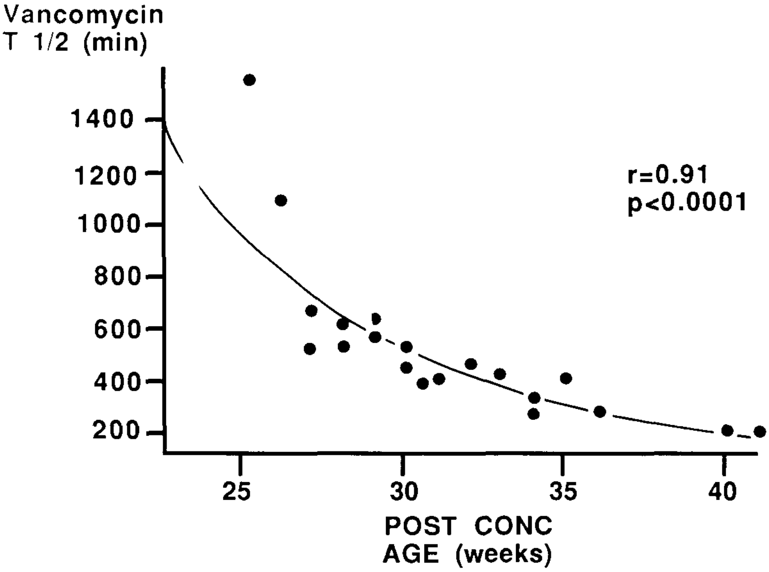

FIGURE 2. Correlation between postconceptional age and vancomycin $t_{1/2}$.

TABLE 7
Recommended Doses and Dose Intervals of Vancomycin in Preterm Infants, to Maintain Mean Steady-State Peak Concentration of 30 mg/l (range of 25 to 40 mg/l) and Trough Concentration of 6 mg/l (Range of <10 mg/l)

	Postconceptional age (weeks)			
	<27	27—30	31—36	>37
Body weight (g)	<800	800—1200	1200—2000	>2000
Daily dose (mg/kg)	18	24	36	45
Dose interval (h)	36	24	12/18	12
Dose/injection (mg/kg)	27	24	18/27	22.5

Note: Mean level assigned to 21 mg/l (mid-interval concentration between 40 and 10 mg/l).

Adapted from James, A., Koren, G., Milliken, J., Soldin, S., and Prober, C., *Antimicrob. Agents Chemother.*, 31, 52, 1987. With permission.

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Chapter 10

TOXICITY OF ANTINEOPLASTIC CHEMOTHERAPY IN CHILDREN

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TABLE OF CONTENTS

I. Introduction 187

II. Antimetabolites 187
- A. Methotrexate 187
  - 1. Background 187
  - 2. Pharmacology 188
  - 3. Toxicity 188
- B. 6-Mercaptopurine 190
  - 1. Background 190
  - 2. Pharmacology 190
  - 3. Toxicity 190
- C. 6-Thioguanine 191
  - 1. Background 191
  - 2. Pharmacology 191
  - 3. Toxicity 191
- D. Cytosine Arabinoside 191
  - 1. Background 191
  - 2. Pharmacology 191
  - 3. Toxicity 192

III. Alkylating Agents 192
- A. Nitrogen Mustards 193
  - 1. Mechlorethamine 193
    - a. Background 193
    - b. Pharmacology 193
    - c. Toxicity 193
  - 2. Cyclophosphamide 194
    - a. Background 194
    - b. Pharmacology 194
    - c. Toxicity 194
  - 3. Melphalan 195
    - a. Background 195
    - b. Pharmacology 195
    - c. Toxicity 195
  - 4. Ifosfamide (Isophosphamide) 195
    - a. Background 195
    - b. Pharmacology 196
    - c. Toxicity 196
- B. Alkyl Sulfonate 196
  - 1. Busulfan 196
    - a. Background 196

- b. Pharmacology 196
- c. Toxicity 197

- C. Nitrosoureas 197
  - 1. BCNU 197
    - a. Background 197
    - b. Pharmacology 197
    - c. Toxicity 197
  - 2. CCNU 198
    - a. Background 198
    - b. Pharmacology 198
    - c. Toxicity 198
- D. Triazene 198
  - 1. Dacarbazine 198
    - a. Background 198
    - b. Pharmacology 199
    - c. Toxicity 199

IV. Antibiotics 199
- A. Anthracyclines 199
  - 1. Background 199
  - 2. Pharmacology 199
  - 3. Toxicity 200
- B. Bleomycin 200
  - 1. Background 200
  - 2. Pharmacology 201
  - 3. Toxicity 201
- C. Actinomycin-D 202
  - 1. Background 202
  - 2. Pharmacology 202
  - 3. Toxicity 202

V. Plant Products 203
- A. Vinca Alkaloids 203
  - 1. Background 203
  - 2. Pharmacology 203
  - 3. Toxicities 204
- B. Epipodophyllotoxins 204
  - 1. Background 204
  - 2. Pharmacology 205
  - 3. Toxicity 205

VI. Enzymes 205
- A. Asparaginase 205
  - 1. Background 205
  - 2. Pharmacology 206
  - 3. Toxicity 206

VII. Hormones 207
- A. Corticosteroids 207
  - 1. Background 207
  - 2. Pharmacology 207
  - 3. Toxicity 208

VIII. Miscellaneous Group Agents 210
  A. Hydroxyurea 210
    1. Background 210
    2. Pharmacology 210
    3. Toxicity 210
  B. Procarbazine 211
    1. Background 211
    2. Pharmacology 211
    3. Toxicity 211
  C. Cisplatinum 211
    1. Background 211
    2. Pharmacology 212
    3. Toxicity 212

Acknowledgment 213

References 213

I. INTRODUCTION

This chapter reviews the common chemotherapeutic agents used in the treatment of childhood malignancies, with particular emphasis on drug-induced toxicity. While cancer is uncommon in childhood, it remains the second leading cause of death in children older than 1 year of age. Approximately 1 in 10,000 children will be diagnosed with a malignancy each year and 50 to 60% may be cured by multimodal therapy, including surgery, radiation therapy, and chemotherapy. Drug-induced toxicities in children may be severe and have been associated with increased morbidity and mortality in the past. Current disease-specific treatment protocols are designed to be less toxic while maintaining efficacy.

The growing child receiving chemotherapy may experience different toxicities than an adult. While the bone marrow and gastrointestinal (GI) tract receive the brunt of acute dose-limiting toxicity, the brain and bones may experience irrepairable chronic toxicity. Some children cured of a malignancy have been left with permanent sequelae caused by chemotherapy. Today, with more potent antibiotics and better blood bank support, bone marrow suppression is being replaced by nervous system damage as the major dose-limiting toxicity of modern aggressive chemotherapy.

II. ANTIMETABOLITES

A. METHOTREXATE

1. Background

The introduction of aminopterin by Farber et al.[1] in 1948 began the dramatic changes that have been seen in the treatment of many pediatric malignancies. Although aminopterin was successful in producing only temporary remissions, Farber et al. were able to show that heretofore untreatable malignancies could, in fact, be at least controlled.[1] Methotrexate (MTX), the methylated form of aminopterin, is widely used today in the treatment of acute lymphoblastic leukemia (ALL), lymphomas, and osteosarcoma and as an immunosuppressive following bone marrow transplantation.

An analog of folic acid, MTX acts primarily by binding to the enzyme dihydrofolate reductase in competition with folic acid.[2] Folic acid, an essential vitamin that acts in the transport of one-carbon groups, is metabolically active in its reduced form. Dihydrofolate is reduced to tetrahydrofolate by the action of the enzyme dihydrofolate reductase, and MTX competes with dihydrofolate for this enzyme. At physiologic concentrations, folate cannot displace MTX from the dihydrofolate reductase enzyme. Dihydrofolate reductase inhibition ultimately leads to a blockage of purine, RNA, and protein synthesis. Proliferating cells are affected in the S phase of the cell cycle. Based on the mode of action of MTX, three mechanisms of MTX drug resistance may be postulated:

1. Increased levels of dihydrofolate reductase which could overcome the intracellular concentration of MTX
2. Decreased binding of methotrexate to dihydrofolate reductase
3. Decreased MTX transport into the cell[3]

2. Pharmacology

MTX is the predominant folate antagonist in clinical use today. It may be given by mouth, intramuscularly, intravenously (i.v.), intrathecally (i.t.), or intraventricularly. Dosage schedule and amounts are widely variable and range from 10 mg/M^2 to 12 g/M^2. Oral MTX is supplied as a 2.5-mg tablet that is well absorbed. If the child is unwilling to take the pill, it may be crushed and placed in applesauce or juice if necessary.

A dose-dependent GI absorption of MTX has been reported.[4] Low-dose MTX (10 to 20 mg/M^2) is reliably absorbed from the GI tract and results in serum levels of 10 μM. With higher doses, the amount absorbed decreases to approximately 50% and leads to unreliable serum levels. MTX is bound to albumin in the serum and may be displaced by other drugs that bind to albumin. Levels of MTX in the blood are measurable by a variety of reliable assays and MTX levels correlate directly with MTX toxicity. The drug crosses the blood-brain barrier poorly, although intrathecal MTX administration may cause arachnoiditis which permits passage of cerebral spinal fluid (CSF) MTX into the blood.

MTX is primarily excreted by the kidneys with approximately 90% excreted in native form.[5] Excretion is dependent upon glomerular filtration and tubular function, which is clinically important in patients with renal disease and in patients on drugs (i.e., penicillin) that compete with the tubular secretory mechanisms.

Intravenous administration of intermediate dose MTX (1 g/M^2) has been used for several years by the Pediatric Oncology Group for the treatment of ALL. Patients are given a 24-h MTX infusion followed by postinfusion hydration and oral leucovorin rescue. MTX levels are obtained at 24 and 48 h postinfusion. Levels less than 2 μM at 24 h and 0.5 μM at 48 h are rarely associated with clinical toxicity.[6] Patients with levels above these guidelines require intravenous hydration, urinary alkalinization, and intravenous leucovorin rescue until the MTX level is below 0.05 μM. Prolonged MTX excretion may be secondary to decreased renal function, a pleural effusion, or other third-space fluid which can act as a reservoir for this drug.

Leucovorin (citrovorum factor) is used to rescue toxicity of intermediate-dose (1 g/M^2) and high-dose (12 g/M^2) MTX infusions. Leucovorin is a reduced form of folic acid which is metabolized to methyl-tetrahydrofolate, which provides a substrate for one-carbon transfer reactions and by-passes the block induced by MTX. Leucovorin may be given by mouth or intravenously. Oral absorption is excellent and metabolism to the active form is complete. Unusual allergic reactions to leucovorum have been documented, but the drug is generally very well tolerated. For patients with prolonged severe MTX toxicity, intravenous thymidine may be given.

3. Toxicity

MTX is most active against proliferating cells and many of its toxicities are predictable, knowing rates of cellular replication. While all cells may be affected by MTX, normal cells with short replication cycles, such as GI, epithelial, and hematopoietic cells, experience the most damage.

When MTX is given orally at 20 mg/M^2/week (without leucovorin), all three cell lines of the hematopoietic system are depressed. Pancytopenia typically occurs 7 to 10 d after receiving MTX. Erythroid precursors show vacuolization within 24 h of MTX administration and reticulocyte counts decrease shortly thereafter. Platelet production is blocked, resulting in modest thrombocytopenia. Similarly, leukocyte progenitors are damaged, resulting in granulocytopenia and lymphopenia. Recovery of the bone marrow usually occurs within 3 weeks after MTX administration.

Acute GI toxicity, including mucositis, oral ulcerations, and bowel inflammation, has been reported. Malabsorption, as determined by D-xylose absorption, is related to the cumulative MTX dose and some cases may progress to clinical sprue.[7] MTX causes a reversible elevation of hepatic enzymes after administration in high doses and causes hepatic portal fibrosis after long-term administration in low doses. Liver biopsy performed in seven children treated for 1.5 to 2.5 years with MTX showed portal fibrosis in four infants.[8] Hepatic fibrosis progressing to hepatic carcinoma has been reported in a child who received daily MTX for 5.5 years.[9]

Effects on the central nervous system (CNS) by MTX may be both acute and chronic. Arachnoiditis, characterized by fever, headache, vomiting, and CSF pleocytosis after intrathecal administration, is reported in a variable number of children and may be an indication for a change of intrathecal dosage. In one study, 61% of 39 children had symptoms of arachnoiditis within 3 d of i.t. MTX administration.[10] Interestingly, concurrent administration of craniospinal irradiation decreased the incidence to 14%, suggesting the involvement of leukocytes in the syndrome. The incidence of arachnoiditis may be decreased with the administration of hydrocortisone and mixing MTX in Elliott's B solution.

A particularly devastating side effect of MTX therapy is leukoencephalopathy which is fortunately uncommonly seen. Patients who develop leukoencephalopathy usually have received aggressive therapy, including intermediate- or high-dose MTX intravenously, intrathecal MTX, and CNS irradiation.[11] This syndrome is characterized by progressive loss of cognitive function and motor ability. Seizures and paraplegia may be seen and white matter gliosis is found in brain biopsy material.

Intellectual changes as a result of MTX administration have been reported. Intellectual testing in 41 children with acute lymphoblastic leukemia treated with intrathecal MTX was not significantly different from a control group of patients treated for rhabdomyosarcoma in which MTX was not used.[12] However, this study is in conflict with studies which evaluated IQ scores in children with cancer which reported a significant difference in the expected IQ scores between the patients and their siblings.[13] Clearly, these are difficult data to interpret considering the myriad of changes that a child with leukemia must undergo during treatment. Rare cases of MTX-induced reversible dementia and fatal progressive encephalomyelopathy also have been reported.

Pituitary-hypothalamic function was studied by Voorhees and collaborators in children with cancer who were receiving several types of treatment which included MTX.[14] Levels of adrenocorticotropin and follicle-stimulating hormone were normal. Growth hormone stimulation tests were abnormal, but these children retained normal linear growth. However, intrathecal MTX in association with cranial irradiation may result in depressed growth hormone levels and a resultant growth failure.[15]

The toxic effects of MTX on the lungs are uncommon and patients may present with nonspecific pneumonitis.[16] Because the patient population treated with MTX has a predisposition to develop pneumonitis secondary to infection causes (i.e., bacterial, viral, and protozoan), the correct diagnosis may be difficult to make. In addition, four patients have been reported with measles pneumonitis who lacked clinical evidence of measles.[17]

MTX causes characteristic changes on the skin and the hair follicles. Alopecia is a frequent and nearly universal sequelae of MTX therapy. Hair regrowth generally occurs after the discontinuation of therapy. An erythematous macular rash is seen in a small number of patients and hypersensitivity to sunlight is common in these children. A Stevens-Johnson-like syndrome also has been reported in patients receiving intermediate-dose MTX. Occular irritation and skin desquamation associated with MTX therapy has been reported.

Osteoporosis has been reported in patients treated with MTX infusions. Joint swelling and fractures are seen occasionally. In patients where calcium and phosphorus metabolism were evaluated, these metabolic studies were normal.[18] In a study of seven children who had multiple fractures, delayed healing and nonunion occurred, suggesting that MTX inhibited osteogenesis.[19]

B. 6-MERCAPTOPURINE

1. Background

6-Mercaptopurine (6-MP) is a purine analog with antiproliferative activity. It differs from the naturally occurring purine guanine by a substitution of a thiol group for the 6-hydroxyl group on the purine ring. It is inactive in its unmetabolized state, but once broken down to its nucleotide form, it competes with other ribonucleotides for incorporation into DNA and RNA.[20] It is considered to be cell-cycle specific for the S phase. 6-MP has been in clinical use for over 30 years and currently is used in children during the maintenance phase of therapy for acute lymphoblastic leukemia and lymphoma.

2. Pharmacology

The most common route of administration of 6-MP is by mouth, although it can be given intravenously. Absorption from the intestine is unpredictable, with between 16 to 50% of the dose entering the systemic circulation.[21] Peak levels occur 30 to 60 min after ingestion. The drug is detoxified in the liver by the enzyme xanthine oxidase and both active and inactive metabolites are excreted in the urine. Because of hepatic metabolism severe hepatic or renal compromise necessitates a dose reduction. 6-MP penetrates poorly into the CNS and is not useful in the treatment of CNS leukemia. Drug resistance by leukemic cells appears to be associated with a decreased activation or increased degradation of 6-MP.

6-MP is oxidized to 6-thiouric acid (an inactive metabolite) which is partially mediated by xanthine oxidase.[22] Allopurinol (a xanthine oxidase inhibitor) is often used to prevent uric acid nephropathy in patients with leukemia at diagnosis. Patients receiving both 6-MP and allopurinol are thus at an increased risk of developing toxicity and the 6-MP dose should be reduced by 75%.[23]

3. Toxicity

Generally the side effects of 6-MP therapy are mild with the usual oral dosage of 50 to 75 mg/M^2/d. Anorexia, nausea, and vomiting are rare, although higher doses may also cause stomatitis or mucositis. More serious GI side effects, such as diarrhea, develop rarely.

The most common side effect of 6-MP treatment is suppression of the bone marrow. Leukopenia and thrombocytopenia generally occur within 2 to 3 weeks after a 5-d course of therapy.[24] Since repeated dosage of 6-MP can have a cumulative effect on marrow toxicity, it is essential that complete blood counts be followed during treatment.

6-MP-induced hepatotoxicity is at least partially dose dependent, and toxicity usually occurs in patients who have received greater than 2 mg/kg of body weight per day. Liver toxicity may present as either hepatocellular or obstructive liver disease with pathologic features of either intracellular cholestasis or parenchymal cell necrosis or both.[25] The serum bilirubin is usually 3 to 7 mg/dl and moderate elevations of the SGOT and alkaline phosphatase occur due to a direct toxic effect of 6-MP. The onset of jaundice usually occurs more than 30 d after the initiation (or dosage change) of 6-MP. Systemic indications of hypersensitivity such as rash, arthralgia, and eosinophilia are uniformly lacking. 6-MP should be used carefully in patients with preexisting hepatic disease and liver function studies should be monitored in patients on daily 6-MP. Concomitant administration of doxorubicin may enhance hepatic toxicity. 6-MP may cause a facial skin rash which usually fades with continued 6-MP therapy.

C. 6-THIOGUANINE

1. Background

6-Thioguanine (6-TG) is an analog of naturally occurring purines and is closely related to 6-MP.[26] Structurally, 6-TG differs from 6-MP only by the addition of an amino group. It also has a similar mode of action to 6-MP and interferes directly with DNA synthesis. 6-TG is used primarily in the treatment of acute and chronic leukemia and non-Hodgkin's lymphoma.

2. Pharmacology

The usual route of administration is by mouth, but 6-TG may also be given intravenously. Its pharmacokinetics is similar to 6-MP. It is poorly absorbed from the intestine and is given between meals to facilitate absorption. The peak plasma level occurs 10 to 12 h after an oral dose. 6-TG is quickly metabolized by the liver, resulting in excretion of 85% of a 6-TG dose in the urine at 24 h.[27] Its detoxification by the liver does not depend on the xanthine oxidase system and concomitant administration of allopurinol does not require changes in the dose of 6-TG.

3. Toxicity

The principal toxic effect of 6-TG is myelosuppression. As with 6-MP, it is necessary to monitor blood counts during therapy. GI toxicity is reported to be much rarer than with 6-MP, although nausea, anorexia, diarrhea, and vomiting may occur.[28] Stomatitis may be seen and if severe may necessitate dosage reduction. Hepatic function testing should be done prior to initiation of therapy, because drug-induced jaundice has been reported in a few patients. In addition, 6-TG has been associated with the occurrence of hepatic vein occlusion.[29] With prolonged therapy, some patients experience mild neurotoxicity manifested by loss of vibratory sense and unsteady gait.

D. CYTOSINE ARABINOSIDE

1. Background

Cytarabine (cytosine arabinoside, Ara-C) was originally described in 1961 and is derived from marine sponges. This compound differs from naturally occurring animal nucleosides by the presence of a beta-hydroxyl group.[30] Ara-C has proven efficacy in treatment of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and lymphoma, but has little therapeutic role in solid tumors.[31]

2. Pharmacology

Ara-C has major effects on the pyrimidine synthesis pathway which is responsible for the production of both cytosine and thymidine.[32] Cytosine is synthesized from deoxycytidine triphosphate and it is at this step that Ara-C executes its major effects.

Ara-C substitutes the sugar arabinosine in its structure for ribose found in naturally occurring deoxycytidine. Its active metabolite, cytosine arabinoside triphosphate (Ara-CTP), may act as a false pyrimidine base and inhibit DNA polymerase. The presence of the hydroxyl group in the beta configuration may cause steric hindrance when it is incorporated into DNA. DNA polymerase, an enzyme which polymerizes the nucleotide bases during DNA replication, may be unable to utilize the aberrant base. As increased incorporation of Ara-CTP into DNA occurs, increased numbers of cells are killed. Cycling cells are susceptible to Ara-CTP and neoplasms with a high mitotic index show increased toxicity to this drug. Ara-C is metabolized by extra- and intracellular deaminases to the inactive form Ara-U, which is excreted by the kidneys. The plasma half-life is approximately 15 min.[33]

Ara-C may be given intramuscularly, subcutaneously, intravenously, or intrathecally. The dose varies from 100 to 6,000 $mg/M^2/d$, with lower doses given as a continuous infusion while the higher doses are given as a bolus every 12 h. Intravenous administration as a bolus results in high plasma levels which purportedly cause less toxicity than a 5-d continuous infusion. High-dose Ara-C has been used to overcome drug resistance in patients refractory to conventional Ara-C doses. A complete remission rate of up to 70% has been reported in patients with AML who were resistant to standard doses of Ara-C.[34]

3. Toxicity

While Ara-C has a number of toxicities associated with its use, the dose-limiting side effects result from damage to the CNS and the bone marrow.[35] Myelosuppression is the acute dose-limiting side effect of Ara-C. Granulocytopenia occurring 7 to 14 d after use is most common. Megaloblastic anemia may occur which is unresponsive to vitamin B_{12} or folic acid. Thrombocytopenia may occur, while lymphopenia is less common. Inhibition of both humoral and cellular immunity are well described.[36]

As the systemic dose of Ara-C has been increased, CNS toxicity has been seen more frequently.[37] Signs of CNS toxicity include seizure, fever, headache, vomiting, and paraparesis. Dunton et al. reported two patients with leukemia who developed ascending paralysis after receiving high doses of systemic Ara-C and low-dose intrathecal Ara-C.[38] At autopsy, spinal demyelination was seen. The development of dyskinesia, motor difficulties, and acute cerebellar ataxia has been reported.[39] With intrathecal administration in combination with other drugs, arachnoiditis may occur. This is characterized by fever, headache, vomiting, and meningismus. At times, chemical arachnoiditis may be difficult to differentiate from infectious meningitis.

GI toxicity includes anorexia, nausea, vomiting, diarrhea, epigastric pain, and mucositis. The mucositis, while most easily visualized in the mouth, is present throughout the GI tract. A flu-like syndrome consisting of fever, conjunctivitis, joint pains, and muscle aches is seen in about 50% of patients. Conjunctivitis, which is infrequent with standard doses of Ara-C, occurs commonly with higher doses of this drug.[40] Artificial tears and topical steroids are useful in reducing ocular damage.

A febrile reaction may be seen in up to 50% of children treated with Ara-C. This drug fever starts during the Ara-C infusion and ends after discontinuation of therapy. Also a macular or morbilliform skin rash may appear during an Ara-C course which fades upon drug discontinuation. Hepatic dysfunction may occur which is characterized by increased liver enzymes and bilirubin. Other rare side effects reported include cardiac arrest, pulmonary edema, and renal failure.

III. ALKYLATING AGENTS

The alkylating agents are a diverse group of drugs united by a common mechanism of action. Included in this group are the nitrogen mustards (mechlorethamine, cyclophosphamide, melphalan, and isophosphamide), the nitrosoureas (BCNU and CCNU), the alkyl sulfonate (busulfan), or the triazenes (dacarbazine). While these drugs are all alkylating agents, each group has its own unique properties, toxicities, and spectrum of antitumor activity.

The chemical properties of the alkylating agents center around the formation of covalent bonds between reacting molecules.[41] The chemical structure of this group of drugs results in the formation of a highly reactive carbonium ion, a strongly electrophilic reactant. In DNA, nucleophilic guanine residues are able to donate electrons to the carbonium ions resulting in the formation of strong covalent bonds (alkylation). Subsequent to alkylation, several reactions may occur. If the drug is bifunctional, i.e., capable of forming two carbonium ions, cross-linking of DNA may occur. Alkylation results in mispairing of bases, gene miscoding, and the production of defective proteins. Dividing cells will eventually undergo cytolysis. Resting cells, while still susceptible to alkylation, do not undergo cytolysis until they begin to divide. Bearing this in mind, the teratogenic effects of these drugs become understandable.

An understanding of the mechanisms of cytotoxicity leads to predictions concerning resistance that certain malignant cells acquire. While frequently clinical resistance to one alkylating agent confers cross-resistance to the whole group, tumors unresponsive to cyclophosphamide CTX may respond to isophosphamide, an isomer of CTX. Drug resistance may occur with:

1. Decreased drug uptake
2. Enhanced DNA repair
3. An increase in a nucleophilic substance(s) able to chelate drug[42]

A. NITROGEN MUSTARDS

1. Mechlorethamine

a. Background

Mechlorethamine (nitrogen mustard) is a derivative of sulfur mustard (war gas) and was one of the first successful antineoplastic agents.[43] It acts as a bifunctional alkylator in a cell cycle nonspecific manner. It has been in clinical use since the 1940s and is used today in combination therapy in the treatment of pediatric Hodgkin's disease. Treatment consists of the MOPP regimen (mechlorethamine, vincristine, oncovin, procarbazine, and prednisone) with or without radiation therapy, dependent on the patient's clinical or pathological stage.

b. Pharmacology

Nitrogen mustard, once reconstituted, is unstable. It should be administered immediately intravenously into a rapidly flowing intravenous infusion. Nitrogen mustard is a potent vesicant and causes necrosis if it leaks out of the vein or if it is spilled onto the skin.[44] Extravasation or cutaneous exposure should be treated immediately with 2 to 4% sodium thiosulfate. Nitrogen mustard has a plasma half-life of less than 10 min and is metabolized with minimal urinary excretion. The usual dose is 6 mg/M^2 once per week administered on day 1 and day 8 of a 28-d cycle (MOPP). Nitrogen mustard does not penetrate the unaltered CNS.

c. Toxicity

The principal toxicities of mechlorethamine are nausea, vomiting, bone marrow depression, and gonadal damage.[45] Within 1 to 2 h after an intravenous administration, mechlorethamine usually causes moderate nausea and vomiting which may last 24 to 48 h. Bone marrow depression manifested by leukopenia and to a lesser extent thrombocytopenia occurs within 10 to 14 d. Generally the bone marrow recovers completely by days 21 to 28 of a cycle.

Mechlorethamine induces thrombophlebitis in the injection vein and causes skin and subcutaneous necrosis when this drug comes in contact with the skin.[46] Hair loss routinely occurs within 2 weeks. GI toxicity manifested by oral ulcers and diarrhea occurs uncommonly.

Hypersensitivity reaction, erythema multiforma, and other skin rashes have been reported. Neurotoxicity and ocular damage have been reported rarely. In contrast to the other nitrogen mustards, CNS toxicity is extremely rare.

2. Cyclophosphamide

a. Background

Cyclophosphamide (CTX) is the alkylating agent most commonly used in pediatric oncology. This agent was designed to be selectively activated by (and selectively toxic to) neoplastic cells. While CTX is a highly efficacious antineoplastic agent, actively proliferating normal cells are damaged by this drug.[47] CTX is effective in the treatment of lymphoblastic lymphoma, leukemia, rhabdomyosarcoma, osteosarcoma, neuroblastoma, and Ewing's sarcoma.

b. Pharmacology

The pharmacology of CTX is incompletely understood because of the large number of active and inactive metabolites produced during CTX degradation. CTX is well absorbed after oral administration with low doses (1 to 2 mg/kg), resulting in virtually 100% absorption.[48] Higher doses give variable absorption. Peak absorption is within 3 h after oral ingestion and reaches a plateau for approximately 10 h thereafter. CTX is inactive until metabolized by the hepatic P450 microsomal enzymes to 4-hydroxycyclophosphamide (4HC) and aldophosphamide. Drugs such as phenobarbital which induce P450 enzymes will shorten the half-life of CTX; however, the clinical efficacy of CTX does not appear to be reduced by more rapid metabolism.[49] Aldophosphamide is metabolized to acrolein (an inactive metabolite) and phosphoramide mustard (a highly active alkylating agent). Metabolites are excreted in the urine and it is felt that acrolein is responsible for the hemorrhagic cystitis induced by CTX. There is little CNS penetration.

c. Toxicity

CTX induces nausea and vomiting in a dose-dependent manner, and CTX doses less than 500 mg/M^2 are better tolerated than higher doses. CTX does not affect stem cells, an important consideration when using this agent for pretransplant conditioning for bone marrow transplantation. CTX is a bone marrow toxin resulting in a white blood cell (WBC) nadir at 5 to 7 d and recovery by days 10 to 14. As with the nitrosoureas, pulmonary fibrosis has been reported with CTX use, although less commonly.

One of the dose-limiting effects of CTX is bladder toxicity which is manifest by hematuria secondary to hemorrhagic cystitis.[50] The concentration and time of contact of CTX with the bladder transitional cells are the important factors in the development of cystitis. Severe cases of cystitis can lead to bladder fibrosis and dysuria. The incidence of cystitis can be reduced by using a program of forced diuresis and frequent urinations. Continuous bladder irrigation and the use of formalin or silver nitrate may also be used to prevent or treat hemorrhagic cystitis.[51]

In the past, pre- and posthydration to prevent CTX-induced hemorrhagic cystitis has been used. In patients receiving high-dose CTX with vigorous hydration, a syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur.[52] In a patient who is well hydrated, who suddenly develops decreasing urine output and increasing urine specific gravities, the possibility of SIADH should be evaluated.

Effects on the gonads are dose and age related with respect to CTX. Younger children (prepubertal) may still remain fertile even after high doses of CTX, whereas postpubertal patients are more likely to be sterile even at lower doses.[53] Ovarian failure and amenorrhea are reportedly commonly, while secondary sexual characteristics are usually preserved. Acute cardiac necrosis has been seen with CTX, but is very rare and usually occurs in the setting of a very high dosage of CTX given over a very short period of time.[54] Kende et al.[55] describe five children treated with high-dose CTX who had transient blurring of vision for up to 2 weeks following administration.

Allergic manifestations are reported with CTX, but are uncommon. These allergic phenomenon include urticaria, anaphylaxis, and pulmonary edema. Profound immune suppression is seen with CTX that is not associated with neutropenia. Inhibition of T and B cell functions and a decrease in serum immunoglobulin levels have been observed.[56] In addition, T suppressor cell function seems to be particularly inhibited. This inhibition of suppressor cells has been particularly useful in treating posttransplant patients exhibiting signs of graft vs. host disease. Alopecia is nearly universal following CTX administration as well. Other unusual toxicities associated with CTX include teratogenesis as manifest by acherica (congenital absence of a hand), hepatic toxicity, and gonadal dysfunction.

3. Melphalan

a. Background

Melphalan (L-phenylalamine mustard, L-PAM) is chemically related to nitrogen mustard and differs by the addition of the amino acid phenylalanine.[57] Its function is similar to nitrogen mustard as well, in that it transfers alkyl groups to cellular proteins resulting in cell death. The additional amino acid group in L-PAM allows transport into cells via specific amino acid pathways. L-PAM has been used to treat multiple myeloma and as part of a prebone marrow transplant cytoreduction regime in children.

b. Pharmacology

L-PAM is commonly given in doses up to 10 mg/M^2/d for 4 to 7 d. Following ingestion, peak plasma levels are reached after 1 to 6 h, but variability exists between patients secondary to incomplete absorption.[58] The half-life approaches 2 h and the drug undergoes extensive metabolism by the liver.

c. Toxicity

The usual dose-limiting toxicity is myelosuppression. WBC and platelet counts usually reach their nadir between 2 to 3 weeks after treatment, with recovery 1 week later.

Dermatologic toxicity has been seen infrequently, including alopecia, dermatitis, and darkening of the nail beds. Anaphylactic reactions occur in approximately 2% of adults receiving intravenous L-PAM, but do not occur when the dose is given orally.[59] L-PAM therapy is usually associated with minimal nausea and vomiting, except in the very large doses used in bone marrow transplantation. Neurotoxicity has been reported only when L-PAM is given as an intracarotid infusion.

A few cases of symptomatic pulmonary toxicity secondary to L-PAM have been reported. However, subclinical pulmonary toxicity may be more common based on autopsies performed on patients with multiple myeloma.[60] There is an association in adult patients receiving long-term L-PAM with the development of acute leukemia.[61]

4. Ifosfamide (Isophosphamide)

a. Background

Ifosfamide (IFX), 3-(2-chloroethyl)2-(2-chloroethyl amino) tetrahydro-2H-1,3,2 oxazaphosporine-2-oxide, was developed in Germany during the 1960s. It is a congener of CTX, differing only in the position of one of the chloroethyl groups.[62] IFX is currently undergoing clinical trials for use in pediatric solid tumors.

Like its analog CTX, IFX is inactive *in vitro*, requiring metabolism by the mixed function oxidase system of the liver. A number of these metabolites have antitumor activity and act as alkylating agents by preventing the incorporation of thymidine into DNA. Pretreatment with phenobarbital, phenytoin, or chloral hydrate, which induce the activity of these enzymes, results in increased alkylating ability in the serum following dosage with IFX.

Clinical trials have shown IFX to have a broad spectrum of activity against human solid tumors.[63,64] Responses have been noted in sarcomas, acute leukemias, lymphomas, and various carcinomas. In pediatric patients, dysgerminomas, Ewing's sarcoma, neuroblastoma, osteosarcoma, primitive neuroectodermal tumors, rhabdomyosarcoma, retinoblastoma, synovial sarcoma, and Wilms' tumor have been shown to respond. The spectrum of antitumor activity has not been demonstrated to differ significantly from CTX.

b. Pharmacology

IFX is usually given as a short intravenous infusion in normal saline. It may also be given as a long (5-d) continuous infusion. When given as a 2.0-g/M^2 single bolus, the half-life of the drug is about 5 to 6 h.[65] Metabolites of the drug persist longer, with alkylating activity of the urine (the primary means of excretion of these metabolites) peaking at 8 to 16 h postdose. IFX apparently is metabolized more slowly than its analogue CTX.

c. Toxicity

The major dose-limiting toxicity of IFX is hemorrhagic cystitis.[66] In patients receiving no uroprophylaxis, 40% are reported to develop this complication. Acrolein, a highly reactive aldehyde metabolite of IFX, is thought to be responsible for bladder toxicity. Forced diuresis remains the mainstay of preventive therapy, but a number of pharmacologic compounds have been suggested to prevent hemorrhagic cystitis. These include sodium bicarbonate, *N*-acetylcysteine, and ascorbic acid. Recent clinical trials have involved the use of MESNA, a compound related to *N*-acetylcysteine. It is given in a low dose intravenously and is almost completely excreted by the kidney, where it is metabolized with the release of a free thiol group. This combines with the 4-hydroxy metabolites of IFX and prevents the formation of acrolein.

Hematologic toxicity is less common and generally consists of leukopenia and rarely anemia and thrombocytopenia. In recent studies, 25 to 80% of patients receiving the drug were noted to develop leukopenia. The nadir occurs at days 7 to 14 and reverses rapidly. Nausea and vomiting occur in over half of the patients receiving IFX. Alopecia is common, with hair loss peaking around day 20. CNS toxicity was noted in 11 of 50 pediatric patients involved in the phase II trial of IFX.[67] The spectrum of neurotoxicity seen in the trial ranged from mental status changes (drowsiness, irritability) to seizures. While most symptoms of neurotoxicity were transient and reversible, some severe morbidity has been reported.

B. ALKYL SULFONATE

1. Busulfan

a. Background

Busulfan (BUS) is a monovalent alkylating agent which does not cross-link DNA. Its mode of action appears to be mediated through binding to thiol groups in amino acids and proteins. This drug is commonly used in the palliative treatment of chronic myelogenous leukemia (CML); however, newer regimens have incorporated BUS for marrow ablation prior to bone marrow transplantation in patients with acute myeloid leukemia.[68] High-dose BUS with CTX has been used for cytoreduction prior to autologous bone marrow transplantation in children with recurrent solid tumors.[69]

b. Pharmacology

BUS is generally given as a single oral dose. After absorption, BUS is metabolized by the liver and metabolites are slowly eliminated from the circulation by excretion in the urine.

c. *Toxicity*

Mild nausea and vomiting commonly follow BUS administration. The dose-limiting toxicity, as with other alkylating agents, is myelosuppression. At low doses, BUS has some selective activity on the granulocytes with relative sparing of the platelets and lymphoid cells. The nadir of myelosuppression occurs after 11 to 30 d with recovery occurring at 1 to 2 months. Blood counts need to be followed closely because patients may develop BUS-induced pancytopenia and aplastic anemia.[70]

BUS was the first antineoplastic agent recognized to cause pulmonary failure. In adults with CML, up to 4% may develop clinical lung toxicity and up to 12% may have histologic changes associated with BUS toxicity.[71] While patients with BUS-induced lung damage generally develop progressive pulmonary failure, a few patients respond to high doses of corticosteroids. Hyperpigmentation occurs in approximately 5% of adults on BUS therapy. In addition, long-term administration of BUS has been associated with testicular atrophy, gynecomastia, cholestatic jaundice, and cataracts.[72] In children receiving high doses of BUS preparation for bone marrow transplantation, seizures have been observed.[69] Prophylactic administration of phenytoin has been recommended during BUS therapy to decrease this side effect.

C. NITROSOUREAS

1. BCNU

a. *Background*

BCNU is an alkylating agent with a chemical structure of 1,3-bis(2-chloroethyl)-1-nitrosourea. It alkylates DNA resulting in the formation of DNA-DNA binding in a cell-cycle nonspecific fashion. BCNU is highly lipid soluble allowing for rapid CNS entry at approximately 30% of the plasma concentration.[73] BCNU may be given orally or intravenously and it has use in the treatment of lymphomas, Ewing's sarcoma, and malignant brain tumors.

b. *Pharmacology*

In aqueous solutions, BCNU spontaneously decomposes, producing chloroethyl carbonium ions which alkylate DNA. Also an isocyanate group is formed which reacts with amines in a carbamoylation reaction. BCNU is administered orally or intravenously in a dose of 60 to 300 mg/M^2 and has an initial half-life of 6 min. BCNU is metabolized by the liver with metabolites excreted by the kidneys.

c. *Toxicity*

BCNU causes nausea and vomiting that may be quite severe, beginning shortly after the administration and continuing for several hours. The nitrosoureas also cause bone marrow suppression and the nadir of pancytopenia may occur 4 to 6 weeks after BCNU therapy.[74] It is not uncommon for patients to have thrombocytopenia 28 d after the BCNU administration. Red blood cell counts are relatively spared; however, leukopenia beginning as late as 3 to 5 weeks is encountered. Bone marrow suppression is the acute dose-limiting toxicity of BCNU, and its effects are often cumulative with delayed recovery following subsequent doses.

BCNU-induced pulmonary toxicity occurs in approximately 5% of adults treated with this drug.[75] The pneumonitis leads to restrictive lung disease which may or may not be reversible, and progressive fibrosis may continue despite drug withdrawal. The causes of progressive alveolitis leading to pulmonary fibrosis are not known; however, the total BCNU dose, the duration of therapy, and the concurrent use of chest irradiation all play a role. Doses greater than 1500 mg/M^2 have been associated with about a 50% incidence of pulmonary toxicity. Signs of pulmonary toxicity include a dry cough, tachypnea, and dyspnea.

The chest X-ray shows interstitial infiltrates, while pulmonary function tests demonstrate hypoxia, a restrictive pattern, and decreased CO_2 diffusion.

Renal toxicity is infrequent after use of nitrosoureas and seems to be dose related.[76] At doses greater than 1500 mg/M^2, however, six of six children had signs of renal failure. Abnormalities of the urinary sediment with proteinuria as well as an increase in serum creatinine may occur 2 years after BCNU administration. Allergic reactions have also been seen, although they are very unusual. Side effects of the CNS include convulsions and drowsiness, which occur more frequently at high doses.[77] BCNU is significantly immunosuppressive apart from its myelosuppressive effects. Rat animal models show that first-trimester exposure to BCNU may be teratogenic, the effects of which are not seen in the later trimesters. In addition, there are several incidences of humans receiving BCNU later in pregnancy with no teratogenicity reported in the offspring. Facial flushing also may be seen with BCNU.

2. CCNU

a. Background

CCNU (lomustine) is a nitrosourea with the chemical structure 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea. It is structurally similar to BCNU and possesses similar toxicities and antitumor spectrum of activity.[78] The primary clinical uses of CCNU are the palliative management of primary and metastatic brain tumors and the treatment of refractory Hodgkin's disease.

b. Pharmacology

CCNU is administered orally and the usual dose is 100 to 130 mg/M^2/d as a single oral dose. Doses should not be repeated more often than every 6 to 8 weeks because delayed myelosuppression is a significant clinical problem. The drug is taken on a empty stomach, and absorption is complete within 60 min. Like BCNU, CCNU is highly lipid soluble and the drug rapidly·crosses the blood-brain barrier. Levels in the CSF are 15 to 30% of simultaneous plasma levels. Metabolism is mediated through the hepatic P450 microsomal enzymes. Metabolites are excreted slowly in the urine and some enterohepatic cycling of CCNU has been demonstrated.[79] Both these facts may explain the delayed toxic effect of CCNU on the bone marrow.

c. Toxicity

Like BCNU, the ingestion of CCNU is associated with moderate nausea and vomiting. The acute dose-limiting toxicity of CCNU is bone marrow suppression. The nadir of the blood count reduction may occur 4 to 6 weeks after dosing. Prolonged thrombocytopenia has been reported. CCNU is often given on an every 6- to 8-week basis to allow for full recovery of the bone marrow.

While the nephrotoxicity of BCNU and methyl-CCNU is well documented, only one case of nephrotoxicity secondary to CCNU has been reported.[75,80,81] With each drug, the insidious onset of renal failure may occur months to years after drug cessation. CCNU, in contast to BCNU, is very rarely associated with pulmonary fibrosis.[82]

D. TRIAZENE

1. Dacarbazine

a. Background

Dacarbazine (DTIC) has limited application in pediatric cancers. Its exact mechanism of action is unknown. Although it is a structural analogue of a purine, its main mechanism of action is not as an antimetabolite. It has some alkylating activity as well and may bind to protein. It has been used in soft tissue sarcomas in children. It also has been used to replace or reduce the amount of procarbazine in therapy of Hodgkin's disease. It has some activity in malignant melanoma.

b. Pharmacology

DTIC is given as an intravenous solution. Because of the instability of the reconstituted drugs, it should be given shortly after the addition of saline or sterile water. Intravenous administration must be done with great care, as extravasation may result in severe skin burns. The solution is also light sensitive, and intravenous solutions should be changed every 8 h. Following intravenous administration, the drug is quickly metabolized by the liver. Only a fraction of the drug is excreted by the kidneys.

c. Toxicity

Severe nausea and vomiting are seen in more than 90% of patients receiving this drug. Myelosuppression is also common, with the nadir of counts being reached around the third week following therapy. Less common is the flu-like reaction which includes myalgias, arthralgias, and fever. Urticarial reactions have also been reported and are rare. DTIC has been shown to be a potent carcinogen in animal studies.

IV. ANTIBIOTICS

A. ANTHRACYCLINES

1. Background

The anthracyclines, doxorubicin and daunomycin, belong to the antibiotic class of antineoplastic drugs and have wide clinical use.[87,88] Daunomycin was the original clinically useful anthracycline and today is used in the treatment of ALL and AML. Doxorubicin, however, is the single most useful clinical antineoplastic agent and is effective in many pediatric malignancies, including acute leukemias, lymphomas, osteosarcoma, Ewing's sarcoma, Wilms' tumor, and neuroblastoma. The efficacy of these drugs is severely limited by their cardiac toxicity which has stimulated interest in the development of new less toxic analogs.

Both doxorubicin and daunomycin are produced by the fungus *Streptomyces peucetius* and are found naturally in various foods such as olives and rhubarb. Both of these drugs share the same tetracyclic ring structure, but differ at the C-14 position where doxorubicin has a hydroxyl group while daunomycin has a hydrogen. Both of these antibiotics bind to DNA and several mechanisms may account for their ability to kill cells.[89]

Low-dose daunomycin and doxorubicin are able to effectively kill cells in the G-2 phase, whereas higher doses kill cells in the S phase. These drugs bind to phosphates of DNA and intercalate between adjoining nucleotide pairs, resulting in altered nucleic acid synthesis and cell death. Another mechanism of cellular toxicity involves the formation of free radicals. Doxorubicin, in the presence of NADPH, is converted to a semiquinone radical which may be oxidized back to doxorubicin and supraoxide. Supraoxide then damages DNA and cell membranes. Supraoxides are detoxified by catalase and glutathione peroxidase. The absence of these protective mechanisms in cardiac muscle may enhance anthracycline toxicity in the heart.

2. Pharmacology

The anthracyclines are given routinely in a dose of 60 to 90 mg/M^2 as an intravenous push over 2 to 3 min. Recently, infusions over 24 to 96 h have been used with reduced GI and cardiac toxicity. Doxorubicin is metabolized by the liver and partially excreted in the bile.[90] In patients with compromised hepatobiliary function, doses should be reduced by 50 to 75% of the usual dose. Daunomycin is also metabolized by the liver, but has more significant renal elimination and doses need to be reduced in patients with hepatic or renal diseases.[91] After intravenous administration, anthracycline metabolites may impart a red color to the urine for several days. The anthracyclines cross the blood-brain barrier poorly. The anthracyclines are incompatible with sodium heparin and dexamethasone phosphate.

3. Toxicity

The main toxicities of the anthracycline antibiotics are hematopoietic, GI, cardiac, and skin, if extravasation occurs. The acute dose-limiting toxicity is myelosuppression, while the chronic dose-limiting toxicity is due to cardiac damage.[92] Myelosuppression typically occurs 7 to 10 d after intravenous administration, with return of the peripheral counts in approximately 3 weeks. Neutropenia and thrombocytopenia are the most common manifestations.

GI toxicity usually seen is mucositis, which may be quite painful and result in a significant reduction in oral intake. Stomatitis often starts as a sublingual burning sensation which progresses to ulceration in a few days. These are particularly troublesome when they occur within radiation ports (radiation recall) and when the patient is neutropenic. Inflammation of the cecum (typhlitis) may occur which can lead to bowel perforation.[93]

The most common dose-limiting toxicity of this drug pair is chronic cardiac damage.[94] In a study by Dearth et al.[95] with a 5-year follow-up, 6 of 112 patients (5.3%) developed congestive heart failure secondary to a dose-dependent cardiomyopathy. Often the onset of cardiac pump failure is insidious and may not respond to digitalis glycosides and diuretics. The cardiac toxicity of the anthracyclines limits the cumulative dose to a maximum of 550 to 600 mg/M^2 over a lifetime. While many patients are able to receive maximal doses, several preexisting conditions may necessitate a reduction of the total dose. Patients at risk for developing early toxicity are those with preexisting heart disease or those with mediastinal irradiation.

Several methods for following the patient's cardiac status have been explored. Echocardiography was investigated as a means of prospectively identifying patients who may develop heart failure. Ramos et al.[96] demonstrated decreased muscle contractility with increasing dosage of doxorubicin by measuring changes in the preejection period (PEP) and left ventricular ejection time (LVET). The PEP/LVET ratio may be a better indicator of impending toxicity because this ratio tends to increase in patients who may develop congestive heart failure. The bulk of the echocardiographic data suggests that it is not a reliable predictor of impending heart toxicity, but may be useful in the follow-up of patients who developed congestive heart failure.

Radionuclide ventriculograms have been studied as a means for identifying patients with impending cardiac toxicity. This test is performed by injecting a radionuclide and then scanning for radio emissions over the heart. Rest and exercise data are obtained and compared, and the fraction of the normal left ventricle volume ejected is recorded. The radionuclide scan is probably the best indicator in pediatircs of imminent anthracycline cardiac toxicity, but in children who are too young to perform the exercise portion of the test, the information may be unreliable.

Anthracyclines will cause extensive local skin and deep tissue damage with ulceration and necrosis if drug extravasation occurs. Prevention is imperative. Anthracyclines may be given through an unquestionable, patent intravenous site. If drug extravasation is suspected, infiltration of the site with hydrocortisone sodium succinate may be helpful. Some patients experience erythematous streaks up the vein with urticaria without evidence of drug extravasation. Anthracyclines induce moderate nausea and vomiting which may be reduced by pretreatment with antiemetics. Both anthracyclines also "reactivate" radiation-induced skin and mucous membrane changes.[97] Alopecia is usually complete with hair regrowth after drug discontinuation.

B. BLEOMYCIN

1. Background

Bleomycin (blenoxane) is actually a mixture of fermentation products produced by *Streptomyces verticillus* and belongs to the antibiotic class of antineoplastic agents. Bleomycin A2, a complex sulfur-containing polypeptide, represents approximately 50% of the drug.

Bleomycin binds to single- or double-stranded DNA and binds to a lesser extent with RNA, with resulting scission of the strand and inhibition of replication.[98] Bleomycin is thought to be cell-cycle specific, having its major action during the G2 and M phases. It inhibits progression out of the G2 phase and for this reason has been used to kinetically synchronize cells for further chemotherapy. It is used in pediatric oncology in Hodgkin's and non-Hodgkin's lymphomas, germ cell tumors, and carcinomas.

2. Pharmacology

A variety of routes have been used to administer bleomycin. It is usually given as an intravenous dose, but can also be given as an intramuscular, intraarterial, intratumor, intracavitary, or subcutaneous injection. After intravenous administration, the plasma concentration peaks in the first half hour and declines over the next 2 to 4 h.[99] It is often given as a continuous infusion, which has been demonstrated to be less toxic than bolus dosage.

The drug is inactivated by intracellular aminopeptidases, which are found in most cells. Interestingly, these enzymes are found in lower amounts in lung, skin, and certain tumors, which probably contributes to the toxicity of bleomycin in these tissues. The drug is eliminated almost entirely via the kidney where over 50% of the dose can be recovered unmetabolized in the urine. In patients with renal compromise, comparable dosage reductions must be made.

3. Toxicity

General symptoms of toxicity following bleomycin administration include headache, mild nausea and vomiting, and pruritus. Over 50% of patients receiving the drug are noted to have some degree of fever. Hypersensitivity reactions have been described, ranging from local cutaneous reactions to life-threatening anaphylaxis.[100] Generally, a test dose of the drug is administered prior to therapy especially to patients with lymphoma.

Pulmonary fibrosis is the most notable toxic effect of bleomycin. Studies done in adults showed that fibrosis appears in approximately 5% of patients who have received a cumulative dose of 400 U. Pulmonary fibrosis induced by bleomycin carries a mortality rate of 1 to 2%. However, in one series of 168 patients, 40% had clinically detectable pulmonary toxicity with a 10% mortality rate.[101] At higher doses, the incidence of significant pulmonary disease rises sharply, but even at lower doses, the appearance of the toxicity is sporadic and cannot be predicted on the basis of dose alone. Also, the pulmonary fibrosis may progress despite discontinuation of the drug.

The appearance of clinical signs of pulmonary toxicity is insidious and usually follows 1 to 2 weeks after administration of the drug. Clinically, the patient usually presents with a dry, hacking cough and complaints of dyspnea. Resting tachypnea may be present and rales may be heard on physical exam. Radiographic studies done at this time usually demonstrate a generalized fibrosis and patchy infiltrates. Pulmonary function tests often demonstrate restrictive lung disease, with arterial hypoxemia and a decrease in the carbon monoxide diffusing capacity. A hypersensitivity pneumonitis related to low doses of bleomycin also has been described.

A variety of tests have been proposed to predict bleomycin lung toxicity or to detect it in its earliest stages.[102] Clinical signs may not be present until significant fibrosis has occurred, and the chest X-ray may lag behind progression of the disease. Pulmonary function testing is usually performed before onset of therapy in order to provide a baseline for further evaluation. Two tests seem to be most sensitive to the toxic changes of bleomycin lung, namely, carbon monoxide diffusing capacity (DLCO) and forced vital capacity. It has been proposed that bleomycin be discontinued when the DLCO falls to 40% of the patient's normal value, but even this will not guarantee that the patient will not progress to clinically significant toxicity.

Concomitant administration of ionizing radiation increases the incidence of pulmonary toxicity in patients receiving bleomycin. Up to 50% of these patients may develop severe pulmonary problems, with a similar rise in mortality. Oxygen therapy, especially during general anesthesia, has also been noted to increase the incidence of pulmonary disease.

The management of pulmonary toxicity generally involves symptomatic relief. Naturally, discontinuation of the drug at the first signs of toxicity is essential. The use of steroids in the treatment of fibrosis is controversial, but often prednisone is given in the hope that it will have some beneficial effect. Prevention of the toxicity by limiting the total dose of the drug, altering the method of administration, and frequent pulmonary testing to detect minimal changes are essential. Investigators are currently screening a number of related compounds that may prove to be as effective as bleomycin, but avoid the toxic pulmonary complications.

The skin represents the most common site of bleomycin toxicity. This is most often manifest by mild stomatitis and alopecia, but generalized hyperpigmentation, edema, and erythema can occur. A severe form of desquamating dermatitis has been described.[103]

C. ACTINOMYCIM-D

1. Background

Actinomycin D (dactinomycin, ACT-D) belongs to the antibiotic class of antineoplastic agents and is produced by a species of the fungus *Streptomyces*. It binds to DNA, prevents transcription of RNA, and potently inhibits protein synthesis.[104] It was found to be too toxic for antibacterial use, but has some remarkable antineoplastic properties. ACT-D intercalates between specific base pairs on DNA in a cell cycle-nonspecific fashion. ACT-D is commonly used in the treatment of childhood sarcomas: Ewing's sarcoma, rhabdomyosarcoma, soft tissue sarcomas, and Wilms' tumor.

2. Pharmacology

ACT-D is administered intravenously and is rapidly removed from the circulation by tissue binding. It has a half-life of approximately 36 h secondary to slow release of ACT-D from tissue binding sites.[105] Most of the drug is excreted unchanged in the urine and the bile. Dactinomycin is commonly used in combination chemotherapy at a dose of 0.5 mg/M^2/d i.v. given daily for 5 consecutive days.

3. Toxicity

The dose-limiting toxicity of ACT-D is myelosuppression with the nadir of leukopenia occurring 7 to 14 d after administration.[106,107] Thrombocytopenia may occur as early as the third day of a 5-d course and daily blood counts should be performed to monitor for early toxicity. After multiple courses, some patients have prolonged thrombocytopenia which persists after leukopenia has resolved. When such patients are treated with prednisone and chemotherapy, the nadir and duration of thrombocytopenia is blunted.[108]

The dose of ACT-D may also be limited secondary to mucositis. Oropharyngeal ulcerations often appear at 7 to 10 d after the start of chemotherapy and may be severe enough to cause dehydration and weight loss. Mucositis may be accentuated in tissues receiving concomitant radiation therapy.

ACT-D interacts with irradiated tissues in a variety of peculiar ways.[97,109] Irradiation therapy administered together with ACT-D may result in enhanced toxicity to the irradiated skin and mucous membranes. Skin reactions occur most frequently and erythema and dry desquamation may be seen after the initial doses of radiation. This reaction may progress to ulceration which may persist for months or years. Local wound healing is poor and skin grafts often fail because of reduced neovascularization. Mucositis induced by ACT-D may be accelerated in areas receiving concomitant radiation therapy and the tissue with the most sensitivity appears to be the esophagus. Also, acute enteritis occurs in up to one third of children receiving both ACT-D and radiation therapy. Radiation-induced nephritis appears also to be enhanced by ACT-D.[110]

ACT-D also may induce severe inflammatory reactions in tissues irradiated months to years previously. Such recall reactions may be life-threatening if vital organs such as the heart, lungs, or liver are the site of the inflammation. The severity of these reactions is difficult to predict based on either drug dose or amount of radiation received. Hepatic toxicity is unusual in children receiving ACT-D unless the liver has been in the field of irradiation. Administration of ACT-D following hepatic irradiation results in prolonged myelosuppression suggesting hepatic damage may alter the half-life of ACT-D.

If ACT-D extravasates, local tissue necrosis occurs. However, phlebitis of the injection vein may occur without drug leakage. Prevention of extravasation is most important and ACT-D should be administered with the special precautions taken for all vesicants.

Vomiting and mild diarrhea are commonly associated with ACT-D therapy. Alopecia occurs within 2 weeks after drug administration and a pustular folliculitis which resembles acne has been reported.

V. PLANT PRODUCTS

A. VINCA ALKALOIDS

1. Background

The two common vinca alkaloids, vincristine (VCR) and vinblastine (VBL), are derived from the periwinkle plant. These alkaloids are spindle poisons which disrupt microtubule formation and arrest cell division during mitosis.[111] VCR and VLB are structurally very similar, but possess different clinical toxicity and antineoplastic effects. VCR is one of the most widely used antineoplastic agents in children. It is used in the induction and maintenance of acute leukemias and is effective in the treatment of most pediatric solid tumors. VBL use in pediatrics is usually restricted to treatment of histiocytosis X, Hodgkin's disease, and germ cell tumors.

2. Pharmacology

VCR and VLB are administered intravenously and each possesses a triphasic plasma disappearance curve.[112] Both drugs are excreted by the liver into the bile with less than 5% of drug appearing in the urine. Biliary obstruction may lead to prolonged drug levels and enhanced toxicity. Thus, many oncologists will reduce the dose by 50% if the serum bilirubin is 1.5 to 3.0 mg/dl and discontinue these drugs if the bilirubin is greater than 3.0 mg/dl.[113] Both drugs bind to tubulin and block the polymerization of soluble dimers to form microtubues. Microtubules are important in mitosis, axoplasmic transport, and some secretory functions in the cell.

VCR is routinely used in a dose of 1.4 to 2.0 mg/M^2/week intravenously. It will cause skin necrosis if it leaks out of the vein and thus should always be given with extreme care. Overdose with VCR (four to ten times the usual dose) or inadvertent intrathecal administration will cause severe neuropathy and death.[114] To avoid such tragedies, the VCR dose should not be at the bedside when intrathecal medicines are being administered.

While VBL and VCR are very similar in structure and function, their antineoplastic spectrum and clinical toxicities are different. The dose-limiting toxicity of VBL is myelosuppression, while the dose-limiting toxicity of VCR is neuropathy. This may be partially explained by the short half-life of VCR of 7 min (compared to half-life of 53 min for VBL) and the prolonged VCR gamma phase of the plasma decay curve. Also, VCR is more lipophilic than VBL which may enhance its neurotoxicity.

3. Toxicities

VCR and VBL share common toxicities. Both cause local necrosis if venous extravasation occurs and both cause hair loss. Both drugs are associated with hyponatremia with excess urinary sodium wasting in association with inappropriate secretion of ADH.[115] Both drugs, in combination chemotherapy, are associated with azospermia in most postpubertal males and irreversible ovarian failure in most adult females.

The vinca alkaloids induce nerve damage manifested by peripheral neuropathies, cranial nerve palsy, autonomic neuropathy, or encephalopathies.[116] The asymptomatic loss of Achilles tendon reflex is the earliest sign of vinca neurotoxicity, usually followed by loss of knee jerks and then parasthesias of the feet and hands. If the drug is continued, the neuropathy usually progresses to muscle pain, muscle weakness, gait disturbances, and foot (or wrist) drop. VCR neurotoxicity is classically symmetrical and generally reversible within weeks to months after drug discontinuation. No specific therapy appears to enhance recovery.

The vinca alkaloid may induce cranial nerve palsies manifested by hoarseness (or aphonia), ptosis, or diplopia. Also, transient cortical blindness associated with VCR therapy has been reported. VCR may cause mild to severe jaw pain within a few hours after administration. This often occurs after the first but not subsequent dose.

The vinca alkaloids induce autonomic neuropathy leading to constipation and abdominal pain. Patients should receive stool softeners and hydrophilic agents with the first VCR dose when this drug is to be administered weekly. Vinca alkaloid also may induce bladder atony and orthostatic hypotension.

Therapy with the vinca alkaloids has been associated with mental changes, confusion, seizures, and coma. Seizures may occur with or without hyponatremia which may be secondary to inappropriate secretion of ADH. VCR neuropathies are likely to be more severe in adolescents than in children and nerve damage may be aggravated by radiation therapy.

Rarely, accidental VCR overdoses have been reported.[114] Patients receiving two to three times the routine dose experience severe neuropathies which may recover. Patients receiving four to ten times the routine dose develop pancytopenia, bone pain, seizures, and coma and may die. Also in patients who receive an accidental dose of intrathecal VCR, severe ascending neuropathy occurs often, leading to death within 3 to 14 d. In addition to neuropathy, VBL causes some specific toxicities not shared with VCR.[117] The dose-limiting toxicity of VBL is myelosuppression.

Leukopenia occurs with a nadir of 4 to 10 d with complete recovery within 7 to 10 d. Anemia and thrombocytopenia occur, but are usually mild. VBL may cause mucositis and enhance the radiation injury to the esophagus and kidneys. Pulmonary toxicity has been reported in patients receiving VBL in combination with neoplastic agents known to cause pulmonary toxicity. Since the signs and symptoms of pulmonary distress occurred within 1 h after the VBL injection, VBL was felt to have a contributory if not causal role in the pulmonary toxicity. In addition, VBL has been associated with Raynaud's phenomenon.

B. EPIPODOPHYLLOTOXINS

1. Background

VP-16 (etoposide) and VM-26 (teniposide) are semisymthetic derivatives of the podophyllotoxin found in the May apple plant, *Podophyllum peltatum*. The plant podophyllotoxins were originally used clinically for the treatment of condylomata acuminata. These two agents have been shown to be active against acute leukemias, lymphomas, Ewing's sarcoma, neuroblastoma, Wilms' tumor, testicular tumors, and brain tumors.[152] VP-16 is used commonly in the treatment of recurrent solid tumors. Clinical research protocols are currently evaluating the use of VP-16 in combination with ifosphamide. VM-26 is an experimental drug which is used in clinical protocols for patients with recurrent acute lymphoblastic leukemia.[153]

2. Pharmacology

The epipodophyllotoxins are both hydrophobic and, hence, nearly insoluble in water. These drugs have a similar chemical structure and differ only in the substitution of a thenylidene group for a methyl group on the glucopyraoside.

Unlike the parent compound, VM-26 and VP-16 do not bind to tubulin. Both drugs are concentrated intracellularly and, since they are hydrophobic, have unequal deposition in various cellular organelles. Both drugs cause breaks in single-strand DNA and inhibit mitochondrial electron transport and cellular respiration. Cells are inhibited from entering the M phase of the cell cycle and recruitment of cells into the S phase occurs.[154]

VP-16 has a biphasic half-life of 2.8 and 15 h. Approximately 15% is excreted in the urine of which 70% is unchanged. VP-16 (15%) is excreted in the stool and the volume of distribution is 30% of body weight. VP-16 is extensively bound to albumin and there is poor CNS penetration.

VM-26 has a triphasic half-life of 45 min, 4 h, and 20 h and is extensively metabolized. A total of 40% is eliminated in the urine, mostly as a metabolite. Other metabolites consist of lactones, hydroxy acids, and aglycones which are excreted in the bile. The drug is also extensively bound to albumin and like VP-16 does not penetrate the CNS.

The usual route of administration is intravenous, both drugs being contraindicated for intraperitoneal, intrathecal, or intramuscular administration. VM-26 and VP-16 are usually given in doses of 100 to 200 mg/M^2 and are used in combination with other agents. The podophyllotoxins are diluted in normal saline, although VM-26 may be given in 5% dextrose. The drugs are given over 30 to 60 min to avoid hypotension which is associated with a rapid infusion. Patients with hepatic dysfunction experience enhanced myelosuppression with VP-16 therapy and doses should be reduced in these patients.[113]

3. Toxicity

The most common side effects of the podophyllotoxins are hematopoietic and GI toxicity. The dose-limiting toxicity of VP-16 and VM-26 is a dose-dependent suppression of bone marrow function.[155] The nadir of leukopenia and thrombocytopenia commonly occurs 16 d after intravenous administration with complete recovery by 21 d. Toxic effects on other aspects of the immune system are relatively mild. Leukopenia may occur earlier if the patient has had prior radiotherapy. GI complaints consist of nausea and vomiting in most patients, and anorexia may last several days. The anorexia may be increased for patients receiving VP-16 orally, suggesting a direct intestinal effect.

Systemic hypotension occurs if VP-16 or VM-26 is given as an intravenous infusion in less than 30 min. Also the podophyllotoxins are vesicants and need to be given through a running intravenous infusion. Phlebitis of the vein used to inject the drug may occur even though appropriate precautions are taken.

While allergic reactions manifested by wheezing and bronchospasm have been reported, these reactions are rare in patients with leukemia or lymphoma. However, in a recent study, 13% of children with neuroblastoma developed acute allergic reactions to VM-26 which were not prevented by premedication with antiallergic drugs.[156] While most patients have no neurotoxicity, transient peripheral neuropathy has been reported with VP-16 which is enhanced by vincristine administration. Other rare toxicities include local allergic reactions, liver dysfunction, fever, and pancreatitis. Single cases of pancreatitis and myocardial infarction have been reported.

VI. ENZYMES

A. ASPARAGINASE

1. Background

There are few antineoplastic agents classified as enzymes in clinical use today. The two most common are L-asparaginase and E-asparaginase derived from *Escherichia coli* and *Erwinia carotovora*, respectively.[118] These drugs are currently used in the treatment of ALL and have some efficacy in chronic myelogenous leukemia, acute nonlymphocytic leukemia, and melanoma. Commonly, asparaginase is used in the induction and consolidation phases of ALL therapy. The L form is employed as the front line drug, while the E form is used when allergies develop to L-asparaginase. The efficacy of these two agents appear to be similar.

Asparagine is a nonessential amino acid that is utilized by cells in the production of various proteins. It is synthesized intracellularly by the transamination of L-aspartic acid. L-glutamine supplies an amino group and the intracellular enzyme L-asparaginase synthetase catalyzes the reaction. Alternatively, a cell may obtain asparagine from the circulating pool found in blood.

Malignant lymphoblasts have a decreased amount of L-asparaginase synthetase and thus are more dependent upon the circulating pool for their requirement of asparagine. Asparaginase is able to deplete the circulating pool of asparagine. Thus, while normal cells continue to synthesize asparagine due to intracellular L-asparagine synthetase, malignant cells become depleted of this amino acid which results in inhibition of protein synthesis.[119]

2. Pharmacology

L-Asparaginase may be given intramuscularly or intravenously. Doses of 600 U/M^2 result in nearly undetectable asparagine levels within a few minutes. L-asparaginase has a volume of distribution equal to that of the intravascular space and does not cross the blood-brain barrier. Asparagine levels in the CNS decrease because they are dependent on the circulating pool. The half-life of asparaginase is biphasic and in nonsensitized individuals is approximately 9 h and 1.5 d. Individuals who have clinically significant anti-L-asparaginase antibodies will exhibit altered half-lives.

Since L-asparaginase deaminates asparagine, the activity of the enzyme may be measured in an ammonia release assay. By definition, one unit of L-asparaginase will release 1 μmol of ammonia in 1 min. Doses of L-asparaginase range from 5000 to 50,000 U/M^2. The drug is supplied as a lyophilized powder which is reconstituted with normal saline or water.

The timing of L-asparaginase administration may be important when it is used in combination with other chemotherapeutic agents. For example, when given prior to methotrexate, it may actually decrease the efficacy of MTX by inhibiting nucleic acid synthesis. Alternatively, when given 24 h after methotrexate, L-asparaginase may act as a form of rescue by halting protein synthesis and blocking MTX action.[120] While these actions occur in controlled culture experiments, the efficacy of various clinical regimens is under investigation.

3. Toxicity

The most serious side effect of asparaginase is related to its antigenicity as a foreign protein.[121] Serious anaphylactoid reactions or anaphylaxis occur in approximately 1 to 10% of patients and are dependent on the route of administration and the dosage. The intravenous route is more frequently associated with severe anaphylaxis compared to the intramuscular route. While serious side effects have occurred with the first injection, they commonly occur after 8 to 15 doses of the drug. In one study, anti-L-asparaginase IgG antibodies were detected in 24 patients. Since these antibodies are able to bind complement, C3d levels were measured and found to be decreased in 7 of 8 patients who had experienced serious toxicity and found to be normal in the remaining 16 patients who were free from toxicity.

Immunologic memory is maintained in patients who have received L-asparaginase in the past. In children treated with L-asparaginase after a 3-year lapse, 28% developed allergic toxicity. Development of serious local or systemic reactions to L-asparaginase requires that the patient be treated with E-asparaginase, and only a small number of children are allergic to both types.[122] Because there is a possibility of anaphylaxis occurring with either drug, asparaginase must not be given unless resuscitative measures are immediately available.

Another common side effect of L-asparaginase therapy is secondary to the inhibition of protein synthesis. Proteins that have a rapid turnover may exceed the ability of the intracellular enzyme systems to manufacture sufficient quantities of asparagine. Changes in plasma concentrations of various proteins involved in the clotting cascade are frequently reported. Commonly, patients receiving L-asparaginase have a prolonged prothrombin and partial thromboplastin time, as well as reduced levels of fibrinogen and factor XI. While most patients are asymptomatic and do not bleed excessively, CNS thrombosis or hemorrhage has been reported. In a series of 35 cases from 11 institutions collected over an 8-year period, 29 patients had CNS events and 2 died. Dural sinus thrombosis also has been reported. Other alterations in protein concentration include decreases in T4, T3, thyroid-binding globulin, and changes in the electrophoretic mobility of von Willebrand's factor.

An uncommon but potentially life-threatening complication of asparaginase therapy is pancreatitis. As an inhibitor of protein synthesis, usual plasma markers of pancreatitis such as elevation of amylase and lipase may not occur. Vomiting, fever, abdominal pain, and an ultrasound showing edema are all helpful in the diagnosis. The reasons for this toxicity are not clear. Localized pain and discomfort from injection are also commonly seen, but do not necessitate withholdance. Other less common side effects include lethargy, somnolence, and EEG changes.

VII. HORMONES

A. CORTICOSTEROIDS

1. Background

Corticosteroids are synthetic congeners of the natural adrenal hormone hydrocortisone (cortisol). The major derivatives used in pediatric oncology are prednisone, methylprednisolone, and dexamethasone. These drugs bind to specific cytoplasmic glucocorticoid receptors and induce inhibition of glucose transport or phosphorylation in malignant lymphoid cells.[125] Prednisone (1-dehydro-cortisone) and dexamethasone (9-alpha-fluoro-16-alpha-methyl-prednisolone) are useful in the treatment of pediatric malignant lymphomas, Hodgkin's disease, and ALL.[126]

2. Pharmacology

Prednisone is the main corticosteroid used in the treatment of children with cancer. It is commonly administered orally, while hydrocortisone is used intrathecally and methylprednisolone is given intravenously. Prednisone is often given in a 21- to 28-d cycle consisting of 40 to 60 $mg/M^2/d$ with doses taken three or four times a day. Prednisone is supplied as 5-, 10-, and 20-mg tablets and is also available in a liquid form. It is usually well absorbed, but cases of erratic and delayed absorption have been reported.[127] In children, peak levels appear in the blood 1 to 2 h following oral ingestion, and the half-life approaches 2 h, which is shorter than the 3.5-h half-life reported in adults.[128] Prednisone is converted to its active form prednisolone by hepatic metabolism which readily occurs even in the presence of liver disease. Prednisolone and its metabolites are excreted in the urine and are measured as 17-ketosteroids.

Small amounts of prednisolone cross the blood-brain barrier, and intrathecal hydrocortisone is effective in the treatment of CNS leukemia. Most patients on a prednisone cycle experience some toxic side effects (Table 1), and in patients who appear to tolerate prednisone unusually well, drug absorption and compliance should be evaluated to determine if adequate drug is being received.

TABLE 1
Complications of Corticosteroid Therapy in Children

Common

Myopathy
Increased appetite
Centripedal obesity
Immunosuppression
Osteoporosis
Hypertension
Sodium and water retention
Hyperglycemia
Behavior disturbances
Suppression of hypothalamus-pituitary-adrenal axis
Cataracts
Eosinopenia
Growth failure
Impaired wound healing
Hyperlipidemia
Striae
Neutrophilic granulocytosis
Lymphocytopenia
Monocytopenia

Uncommon

Aseptic necrosis of bone
Vertebral compression fracture
Peptic ulceration
Intestinal perforation
Pancreatitis
Pseudotumor cerebri
Glaucoma
Hypersensitivity reaction

3. Toxicity

The multiple chronic side effects of corticosteroids are listed in Table 1. Side effects will be discussed as they occur in children with ALL who are usually treated with multiagent chemotherapy, including 40 to 60 $mg/M^2/d$ of oral prednisone for 28 d. Many patients also receive monthly cycles of prednisone (concomitant with other maintenance drugs such as 6-MP and MTX) every 3 to 4 months during maintenance therapy.

Corticosteroids affect the musculoskeletal system in multiple ways. A direct myopathy occurs leading to a decreased work capacity of striated muscles resulting in easy fatigability and generalized weakness. The proximal muscles are more prominently affected and the myopathy is gradually reversible following discontinuation of therapy. A generalized osteoporosis also occurs with the axial skeleton affected more prominently. In children, osteoporosis is enhanced by immobilization and low calcium intake. Efforts need to be made to maintain an adequate calcium intake as low intake may progress to spontaneous vertebral compression fractures.

Corticosteroids appear to be one of the factors associated with idiopathic aseptic bone necrosis.[129] Patients often complain of bone pain — a symptom common in recurrent neoplasia. Aseptic bone necrosis occurs primarily in the humerus and femur. The incidence of this complication in children with neoplasms appear to be increasing, and recent reports suggest an association with the aggressiveness of the chemotherapy regimen used.[129]

Corticosteroids have multiple effects on the immune system.[130] In general, a neutrophilic granulocytosis occurs secondary to early release of granulocytes from the bone marrow and stimulates production of myeloid progenitors. Lymphocytopenia, monocytopenia, and eosinopenia occur secondary to a direct toxic effect of corticosteroids on these cells. The effect on thrombocytopoiesis is less clear, with both thrombocytosis and thrombocytopenia being reported with chronic steroid therapy. Thrombocytopenia secondary to prednisone in children with cancer is decidedly rare. Corticosteroids tend to increase both the hemoglobin and red cell content of the blood, as evidenced by the hemoglobin rise associated with a prednisone pulse in children on maintenance therapy.[131]

Despite the stimulatory effect of prednisone on granulopoiesis, prednisone therapy is associated with generalized immune suppression. Chronic corticosteroid therapy is associated with an increased incidence of bacterial, viral, fungal, and protozoal infections. In children with malignancies on daily therapy, the mouth and GI tract often colonize with *Candida albicans*. Nystatin prophylaxis will reduce but not eliminate this problem. Trimethaprim/sulfamethazole prophylaxis against *Pneumocystis carinii* pneumonia is a part of most treatment protocols for childhood malignancies which contain prednisone. Because corticosteroids may subdue all signs of inflammation (including fever), such infections as abscess and meningitis may be difficult to diagnose in their initial stages. Also, reactivation of tuberculosis has been associated with corticosteroid therapy. In children with cancer who have a positive tuberculin skin test and who will receive prolonged prednisone therapy (greater than 1 month), close follow-up with cultures and chest X-rays as well as INH prophylaxis for 1 year is recommended.

A clinically beneficial side effect of corticosteroid therapy is appetite stimulation. After 1 to 2 weeks of oral prednisone, the patient's appetite improves and food intake may be dramatic. Children with cancer often lose weight prior to diagnosis, and the nausea, vomiting, and anorexia associated with chemotherapy may result in a 10 to 20% weight loss. Prednisone stimulation of the appetite usually occurs 1 to 3 weeks after initiation of oral therapy, and children may gain 10 to 20 lb during a 28-d prednisone cycle.

Chronic corticosteroid therapy induces multiple cosmetic changes. Even without appetite stimulation and weight gain, fat distribution is altered leading to centripedal obesity. There is a gain of fat in the back of the neck (''buffalo hump''), supraclavicular area, and face (''moonface''), with a concomitant loss of fat from the extremities. Hirsuitism, thinning of the skin, striae, acne, and telangiectasia all can occur. Such cosmetic changes can be most disturbing to the adolescent and appear to be a major hindrance to drug compliance.

Ocular hypertension has been reported in patients on corticosteroids, which is generally reversible with discontinuation of the drug. Posterior subcapsular cataracts occur in up to one third of all patients. These cataracts are rarely optically significant.

Corticosteroid therapy is associated with hyperglycemia and glucosuria.[132] In children with ALL who also receive asparaginase during induction therapy, the incidence of hyperglycemia (fasting plasma glucose greater than 140 mg/dl) approaches 10%. Risk factors include children 10 years old or older, Down's syndrome, and obesity. Hyperglycemia usually occurs within the first week of ALL therapy and is rarely associated with ketosis and acidosis. Therapy does not differ from control of classic diabetes mellitus except that glucose metabolism often returns during prednisone therapy.

Peptic ulcers are rare in children secondary to steroid therapy alone, but ulceration is a problem with or without steroids in the stressful situations associated with pediatric ICU care. The routine use of cimetidine/Mylanta® therapy in children on steroids in an ICU environment is recommended. Pancreatitis occurs with an increased frequency in children on steroids alone and in children treated concomitantly with asparaginase. Corticosteroids are associated with intestinal perforations in patients with underlying chronic bowel disease and may enhance inflammation of the cecum (typhlitis) induced by doxorubicin.

Prednisone causes sodium and water retention with the concomitant enhanced excretion of calcium and potassium.[133] Since fluid retention may lead to hypertension, leukemic patients are often advised to use a no-added-salt diet. Chronic corticosteroid therapy suppresses the hypothalamic-pituitary-adrenal axis and may lead to adrenal atrophy. Rapid withdrawal from chronic prednisone therapy may induce ''steroid withdrawal'' manifested by anorexia, malaise, nausea, vomiting, headache, lethargy, orthostatic hypotension, and myalgia. In acute stress situations (i.e., emergency surgery) in patients who have received steroids in the past, stress coverage for 5 to 7 d is usually recommended.

Psychiatric disturbances ranging from euphoria to frank psychosis have been observed with prednisone therapy.[134] Depression may also occur, and these personality changes are reversible after discontinuation of therapy. Rare cases of steroid-induced pseudotumor cerebri have been reported in children.

VIII. MISCELLANEOUS GROUP AGENTS

A. HYDROXYUREA

1. Background

Hydroxyurea, an analogue of urea, was initially synthesized approximately 100 years ago. It has limited clinical use in pediatrics, but may be of benefit in treatment of chronic myelogenous leukemia (CML), a rare pediatric disorder. There have been reports in the literature suggesting that hydroxyurea may augment cell kill when used in conjunction with radiation therapy.

2. Pharmacology

Hydroxyurea is a water-soluble compound with the molecular weight of 76. Hydroxyurea putatively inhibits DNA synthesis by acting on ribonucleotide synthetase and blocks cell cycle progression through G_1.[135] This enzyme is important in the reduction of ribonucleotides to deoxyribonucleotides. Hydroxyurea apparently binds to the ribonucleotide synthetase in a nonreversible manner which thus inhibits enzymatic reductive capacity. Cells are thus unable to synthesize DNA, although RNA and protein synthesis are unimpeded at least for a limited time. Iron may reverse the effects of hydroxyurea as does the exogenous infusion of deoxyribonucleotides. Other DNA changes, such as fragmentation and template destruction, have also been reported as possible mechanisms of action for this drug. By these mechanisms, cells are synchronized between the G-1 and S phases. Many cell lines show increased radiosensitivity or susceptibility in the G-1 phase and this may account for the *in vitro* observation that the combination of radiation and hydroxyurea results in increased cell kill.

Hydroxyurea may be given by mouth or intravenously as either a rapid push or over a prolonged infusion.[136] Cytotoxicity is dependent upon the concentration and duration of exposure to the drug. The half-life is approximately 4 h with drug eliminated by the kidney. Approximately 50% of the drug is excreted in the active form. Metabolism of the drug in the liver results in the production of urea and carbon dioxide. Absorption after oral administration is good with peak levels occurring approximately 2 h after ingestion. Hydroxyurea does cross the blood-brain barrier.

3. Toxicity

As with most therapeutic agents, myelosuppression is a major dose-limiting effect. Leukopenia occurs approximately 10 d after use, with anemia and thrombocytopenia being less common side effects. Megaloblastic changes occur in the erythroid cell series, which are unresponsive to vitamin B_{12} or folic acid therapy.[137]

Nausea, vomiting, constipation, diarrhea, and stomatitis are also common side effects, but are usually tolerable. A maculopapular skin rash and hyperpigmentation may occur.[138] Less common side effects include azotemia, headache, hallucinations, and convulsions. Alopecia, hepatic dysfunction, allergic reaction, and gonadal damage have been reported.[139]

While hydroxyurea has limited use in pediatrics, clinical usage is indicated in the treatment of chronic myelogenous leukemia, in both the juvenile and adult forms, and in patients with acute nonlymphocytic leukemia who present with greatly elevated WBC counts (greater than 200,000). Hydroxyurea has the ability to rapidly lyse WBCs and is clinically useful in treating patients with leukemia who have a very high WBC count.[140] In this setting, great care must be exercised because the rapid lysis of WBCs may result in the appearance of tumor lysis syndrome. Adequate urine output, alkalinization of the urine, and use of allopurinol should all precede the use of hydroxyurea in a patient with an elevated WBC count.

B. PROCARBAZINE

1. Background

Procarbazine (*N*-methyl hydrazine, PCZ) has a long history of use in the treatment of Hodgkin's disease.[141] Despite this, the exact mechanism of action of this drug has not been elucidated. Both autoxidation of the drug in solution as well as further metabolism *in vivo* are probably important for the chemotherapeutic effect. Cell damage probably results from disruption of protein, DNA, or RNA synthesis. In addition to Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and brain tumors have responded to treatment with PCZ.

2. Pharmacology

PCZ is usually administered orally, but has been used in investigational protocols in an intravenous form. Absorption is rapid and nearly complete by the oral route. PCZ readily crosses the blood-brain barrier and equilibrates in the CSF.[142] PCZ is metabolically activated to a number of toxic derivatives. The antineoplastic activity of PCZ is related to production of alkylating intermediates and free radicals which cause DNA damage. Information about the clinical pharmacology of PCZ is incomplete because of the instability of the drug metabolites formed *in vivo*.

A variety of potential interactions with foods and other drugs make appropriate pretherapy counseling essential. PCZ may interfere with the metabolism of sedative, hypnotic drugs and potentiate the sedative effects of phenothiazines, barbiturates, and narcotics. PCZ is a mild monoamine oxidase inhibitor and may cause acute hypertension in patients taking tricyclic antidepressants or sympathomimetic agents or after ingestion of foods high in tyramine, such as bananas, ripe cheeses, red wines, dark beers, and yogurt.[143] Also, patients who ingest alcohol while taking PCZ may experience facial flushing, headaches, and sweating.

3. Toxicity

A variety of toxic symptoms may be seen with initial therapy, including anorexia, nausea, and diarrhea. Most of these are self-limiting and disappear with continued therapy. A more serious flu-like syndrome has been described, with myalgias, fevers, chills, and lethargy, which is also self-limiting.

Myelosuppression is the most common dose-limiting toxicity. The nadir of platelet counts may be up to 4 weeks after therapy, with red and white cell counts following closely. For this reason, it is essential to follow blood counts during therapy.

More serious, but much less common, are the CNS toxicities which have been described with PCZ.[124] Patients may experience paresthesias, neuropathies, dizziness, ataxia, and/or headache. Up to one third of the patients may experience nightmares, depression, nervousness, or hallucinations, but these stop with discontinuation of the drug. More serious CNS toxicity, including tremors, seizures, or coma, necessitate immediate discontinuation of the drug.

Gonadal function is also adversely affected with drug therapy. Azoospermia and amenorrhea are common in patients treated with high dosages of the drug. Long-term fertility may be adversely affected, although sexual development during puberty seems to be unaffected.[144] Finally, PCZ has been shown to have carcinogenic potential and teratogenic effects in laboratory animals.

C. CISPLATINUM

1. Background

cis-Diamminedichloroplatinum II (CDDP, *cis*-platinum, or platinum) was developed in the early 1960s, when it was observed that platinum compounds, particularly in the presence of chloride and ammonium ions, inhibited the growth of certain bacteria. It belongs to a unique category of chemotherapeutic agents containing heavy metals which are thought to act as a bifunctional alkylating agent, binding to DNA, causing an alteration in its structure and probably resulting in breakage of the DNA strand.[145] The most common use of CDDP has been for solid tumors in adults, which has led to its application in children, where it has been used most often in solid tumors, i.e., testicular and other germ cell tumors, neuroblastoma, Wilms' tumor, osteosarcoma, and tumors of the CNS. CDDP has also been used in childhood carcinomas.

2. Pharmacology

CDDP is given intravenously, either as a bolus dose or infused over a period of time. In the plasma, it binds readily to proteins, with as little as 10% of the drug free in the circulation.[146] Only nominal amounts of the drug have been noted in the CSF, but it has been observed to accumulate in CNS tumors. The half-life of the active form of the drug is 1.3 h in children. Elimination of the drug is via the kidney, with a rapid phase within the first hour of treatment and a more prolonged phase which may last 2 to 4 d.

3. Toxicity

The major dose-limiting toxicity of CDDP is nephrotoxicity.[147] This may range from mild asymptomatic elevation in the BUN and creatinine to life-threatening renal failure. Evidence of kidney damage is usually noted within 10 to 20 d following administration of the drug. The mechanism of damage is not known, but pathological examination of the kidneys of patients receiving the drug shows renal tubular necrosis with relatively normal glomeruli. The presence of preexisting renal disease or concurrent administration of nephrotoxic antibiotics exacerbates the severity of the CDDP-associated nephrotoxicity. Renal damage is also more likely when the drug is delivered as a bolus dose and in patients with high cumulative exposure to the drug.

While serum BUN and creatinine may become abnormal over the course of therapy, these parameters are not an accurate reflection of the diminished renal function associated with CDDP. The 24-h urine creatinine clearance should be obtained as a baseline prior to initiation of drug treatment and followed during therapy.

A variety of maneuvers have been proposed to decrease the incidence of renal damage associated with exposure to platinum. The mainstay of prevention has been forced diuresis, with either increased fluids or mannitol.[148] The use of chloride-containing solutions such as normal or even hypertonic saline has been recommended with the demonstration of decreased nephrotoxicity. Furosemide has also been used to maintain a brisk diuresis, but animal studies have failed to substantiate a protective effect and thus furosemide use remains controversial. A variety of drugs have been proposed, including sodium thiosulfate and probenecid, which may decrease the toxic effect of CDDP on the kidneys, but until the exact mechanism of renal damage has been elucidated, the use of these drugs remains controversial.

In addition to the long-term renal problems associated with CDDP infusion, the loss of magnesium and calcium via the urine may pose clinical problems.[149] The drug appears to decrease the ability of the renal tubules to reabsorb magnesium, with the secondary loss of calcium. Concurrent administration of magnesium with the chemotherapy generally prevents the life-threatening tetany that may result.

Nausea and vomiting are almost universally associated with CDDP therapy. While these side effects generally subside within 1 to 2 h following the infusion, it has been known in some cases to continue for several days. In addition, children may experience nausea and anorexia for 7 to 14 d. Longer infusion times may decrease the severity of this side effect. Antiemetics and sedation are not always effective in preventing vomiting.

Among the neurologic toxicities associated with CDDP therapy, ototoxicity is the most common and best described.[150] The hearing loss associated with the drug is sensori-neural in nature and usually involves high-frequency pure tone loss. The appearance of this complication is related to the cumulative platinum dose. Unlike the nephrotoxicity, the ototoxicity does not seem to be decreased by saline diuresis. Audiometry should be performed at the initiation and throughout therapy to document the degree of hearing impairment.

The occurrence of peripheral neuropathy associated with platinum therapy is small. Generally, this has been described as symmetrical, bilateral sensory loss, involving both the upper and lower extremities: the ''stocking and glove'' distribution. Motor disturbances are much less common, but may include gait perturbations or increased clumsiness. These symptoms improve with the cessation of therapy.

In rare cases, more serious neurological side effects have been described. Papilledema and retrobulbar neuritis have been observed in association with CDDP therapy, without evidence of tumor involvement. This may not be surprising, since both have been reported with heavy metal poisoning. The occurrence of seizures associated with platinum therapy is extremely rare. Recent applications of platinum treatment to CNS tumors, some of which involve arterial infusions, have been associated with more serious CNS side effects.

Myelosuppression has been commonly associated with treatment with CDDP. The degree of myelosuppression is dose related, but relatively mild, with counts reaching their nadir at day 14 and recovering by day 21.

The occurrence of anaphylaxis with intravenous platinum infusion is a rare but potentially life-threatening complication of therapy. Cholestasis, potentially associated with jaundice, has been reported to occur rarely with CDDP therapy.

A number of drugs that are related to cis-platinum have been developed, with the idea that modification of the chemical structure may decrease the incidence of toxic side effects, particularly nephrotoxicity. Two of these drugs are currently undergoing evaluation: carboplatin and *cis*-dichloro-*trans*-dihydroxy-bis(isoprophylamine) platinum (CHIP). Both are believed to have less nephrotoxic potential, but their antitumor activity is presently being evaluated.

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Chapter 11

BARBITURATE AND NONBARBITURATE SEDATIVE HYPNOTIC INTOXICATION: AN OVERVIEW

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TABLE OF CONTENTS

I. Introduction 222

II. Benzodiazepines 222
    A. Pharmacology and Pharmacokinetics 222
    B. Toxicology 223

III. Barbiturates 224
    A. Pharmacology and Pharmacokinetics 224
    B. Manifestations and Treatment of Barbiturate Intoxication 225

IV. Toxicity with Other Nonbarbiturate Sedative Hypnotic Agents 227
    A. Ethchlorvynol 227
    B. Glutethimide 228
    C. Meprobamate 229

V. Conclusion 229

References 229

I. INTRODUCTION

Drug overdose, either accidental or intentional, continues to account for a significant proportion of emergency room visits and hospitalizations each year. By nature of their legitimate and illegitimate use, pharmacologic agents, such as barbiturates, benzodiazepines, and other nonbarbiturate sedative-hypnotics, persist in being implicated in many poisonings each year worldwide. While the majority of data on both the clinical presentation and treatment of ingestions of these compounds is derived from the adult population, some data are available in children. In this chapter, we will attempt to summarize the approach to the diagnosis and treatment of toxic ingestions of barbiturate and nonbarbiturate sedative-hypnotic agents.

II. BENZODIAZEPINES

Traditionally, the barbiturates have represented the main agents of the medical community for use as both sedatives and hypnotics. The development of benzodiazepines, however, has revolutionized this important therapeutic area, providing in most cases superior pharmacologic alternatives to the barbiturates. Benzodiazepines are safer and, at a minimum, at least as effective as barbiturates.[1,2] These desirable attributes serve to underscore and support the widespread clinical use of these compounds. Since the synthesis of the basic benzodiazepine molecule in 1933, multiple chemical modifications have been performed, modifying their central nervous system (CNS) activity, potency, and bioavailability.[3] Table 1 outlines many of the analogs of these compounds available for clinical use. However, despite their favorable characteristics, the clinician must recognize the potential for morbidity and mortality following overdose with the benzodiazepines.

A. PHARMACOLOGY AND PHARMACOKINETICS

Although large variations exist in the disposition characteristics of various benzodiazepine analogues, pharmacologically they are very similar due to their direct effect on the CNS. The pharmacologic action of benzodiazepines is mediated through specific benzodiazepine receptors found in the limbic, thalamic, and hypothalamic regions.[4] These receptor interactions give rise to the anxiolytic, sedative, hypnotic, skeletal muscle relaxant, and anticonvulsant effects of these agents. As with many other centrally acting pharmacologic agents, such as the narcotic analgesics, the acute discontinuation of these agents following chronic use (more than 6 months) may result in a syndrome of physical withdrawal. In patients receiving chronic therapy, the administration of specific benzodiazepine antagonists such as flumazenil may also give rise to this syndrome of drug withdrawal.[5]

The various benzodiazepine analogues vary widely in their pharmacokinetic properties. Following oral administration, they are well absorbed from the gastrointestinal (GI) tract. Clorazepate dipotassium is rapidly decarboxylated in the GI tract and absorbed primarily as desmethyldiazepam (nordiazepam, the active metabolite of diazepam). In contrast, chlordiazepoxide and oxazepam may take several hours for complete absorption to occur, thus delaying the time of the peak serum concentration. Flurazepam and prazepam undergo significant hepatic first pass metabolism, forming active metabolites. The presence of stomach contents or a decrease in gastric emptying time may significantly reduce or delay the absorption of benzodiazepines. When administered via the intramuscular route, water-soluble agents such as midazolam and lorazepam are completely and rapidly absorbed, while water-insoluble agents such as diazepam and chlorodiazepoxide may be erratically and slowly absorbed.

In general, benzodiazepines distribute widely into most body compartments with distribution dependent on both lipid solubility and protein binding. As a result of their ability

TABLE 1
Benzodiazepines

Generic name	Brand name
Alprazolam	Xanax®
Chlordiazepoxide	Librium®
Clonazepam	Klonopin®
Clorazepate	Tranxene®
Diazepam	Valium®
Flurazepam	Dalmane®
Halazepam	Paxipam®
Lorazepam	Ativan®
Midazolam	Versed®
Oxazepam	Serax®
Prazepam	Centrax®
Temazepam	Restoril®

to distribute into the CNS rapidly, the onset of sedative, anxiolytic, and anticonvulsant effects is rapid, particularly following intravenous administration.

All currently available benzodiazepines are extensively metabolized (either through preparative or conjugation reactions) in the liver, with some having active metabolites. The metabolic pathways involved in the metabolism of benzodiazepines include demethylation, dealkylation, hydroxylation, glucuronidation, and sulfation. While elimination half-lives ($t_{1/2}$) of parent compounds range from 2.7 (triazolam) to 50 h (diazepam), the $t_{1/2}$ for active metabolites range from 2 (*N*-1-hydroxyethylflurazepam) to 200 h (desmethyldiazepam). Thus, the duration of pharmacologic effect cannot be accurately quantitated or predicted from the $t_{1/2}$ of the parent compound alone. This is an important consideration in assessing appropriate dosing intervals for chronic therapy, for assessment of the potential for drug toxicity, and for the development of treatment following intoxication.

B. TOXICOLOGY

While clinically important toxic reactions to benzodiazepines are believed to occur much less frequently than to the barbiturates, there is no question that these compounds have the potential for causing serious morbidity and mortality. Patients intoxicated with benzodiazepines often present with lethargy, sedation, and altered mental status. Occasionally, respiratory embarrassment and suppression of respiratory drive may occur, necessitating intubation and mechanical ventilation. Common belief has it that the large therapeutic to toxic ratio of benzodiazepines affords them the general safety aforementioned. However, with the introduction of more potent agents, this fact may be less true with patients being at risk for drug toxicity at doses significantly closer to those used therapeutically.[6] Additionally, in the presence of ethanol, the toxic effects of benzodiazepines appear to increase dramatically, most likely through enhanced benzodiazepine binding at CNS receptor sites.[7,8]

Until recently, supportive care was the mainstay in the treatment of benzodiazepine intoxication. Drug removal through gastric lavage or ipecac-induced emesis should be instituted with caution and be dependent upon the patient's level of consciousness. Activated charcoal to reduce the absorption of drug from the GI tract is the primary approach to treatment. To date, no data exists, however, on the use of repeated doses of activated charcoal to act as a "GI dialysis" agent in benzodiazepine overdose. However, this approach to charcoal therapy would appear prudent for those intoxications involving benzodiazepines, since there is a significant component of hepatic alteration and detoxification and, in all likelihood, enterohepatic recirculation. Due to the extensive metabolism of these compounds, forced diuresis, attempts at urinary alkalinization, or hemodialysis are of limited benefit in the treatment of toxic benzodiazepine ingestion.

More recently, benzodiazepine antagonists have been synthesized and are currently under investigation in the treatment of both single-agent and mixed-drug overdoses.[9,10] Flumazenil (Ro15-1788) is a 1,4-imidazobenzodiazepine with highly specific and competitive antagonist activity at the benzodiazepine receptor.[11,12] Additionally, flumazenil possesses only limited intrinsic agonist activity. Recent data suggest that this benzodiazepine antagonist significantly increases the level of consciousness following both benzodiazepine alone and mixed benzodiazepine drug ingestion as compared to placebo.[10] Flumazenil also reverses the CNS depression observed in ethanol intoxication, but has no effect in either barbiturate or tricyclic antidepressant overdose. Flumazenil and related compounds appear very promising in reversing the CNS depressant effects of benzodiazepines and may reflect the future approach to the treatment of serious benzodiazepine intoxication.

III. BARBITURATES

Both the clinical use and the incidence of intoxication with barbiturates have been on the decline in recent years.[13,14] This decline is most likely a combined result of the following factors:

1. Introduction of nonbarbiturate sedative hypnotics
2. Increased awareness by the medical community of barbiturate toxic potential
3. Increased state and federal regulation of this group of drugs

This decrease in the clinical use of barbiturate compounds appears fortunate, as the barbiturates represent one of the most lethal classes of sedative hypnotic agents.

A. PHARMACOLOGY AND PHARMACOKINETICS

Barbituric acid was first synthesized in 1864 as a product of condensing malonic acid and urea. While this compound possesses no central depressant activity, substitutions at the 5 position confer sedative hypnotic properties. Substitution of a sulfur for the oxygen atom at position 2, which produces a thiobarbiturate, gives the compound a greater degree of lipid solubility. This increase in lipid solubility is associated with a decrease in the onset of action of the drug. Historically, barbiturates have been classified based on the duration of action of the analogue which can be directly correlated to the lipid solubility of the agent.

All barbiturates depress synaptic responses, delay synaptic recovery, and decrease postsynaptic recovery in the CNS. These pharmacologic effects are most likely mediated through decreasing presynaptic neurotransmitter release along with augmentation in the activity of gamma-aminobutyric acid (GABA).[15,16] Barbiturates may result in decreased brain oxygen use by as much as 50%, with a concomitant increase in glycogen and high energy phosphate content.[17,18] These effects relate to decreased neuronal activity.

Barbiturates can induce substantial changes in a patient's respiratory drive. These effects are rarely observed until the dose exceeds by threefold the "usual" therapeutic dosage range.[19] Insensitivity to carbon dioxide stimulation of the respiratory drive with resultant control dependent on hypoxic drive may result from these agents. As serum concentrations continue to rise, and hypoxic drive to respiration will ultimately fail and result in respiratory failure. Barbiturates are also capable of inhibiting smooth muscle activity, which may result in coughing, hiccoughing, and laryngospasm. Barbiturates exert limited pharmacologic effects on other organ systems when used in usual therapeutic doses. However, they have been noted to decrease both the tone and amplitude of the rhythmic contractions throughout the GI tract.

The pharmacokinetics of barbiturates are markedly influenced by substitutions added to the basic barbiturate nucleus. Oral administration of the sodium salts of barbiturates results

TABLE 2
Barbiturate Classification

- Long acting
  - Mephobarbital
  - Methabarital
  - Phenobarbital
- Short-to-intermediate acting
  - Amobarbital
  - Butabarbital
  - Pentobarbital
  - Secobarbital
- Ultrashort acting
  - Hexobarbital
  - Methohexital
  - Thiopental

in rapid and complete absorption from the small intestine. Administration with food will delay the rate of absorption without affecting the extent of absorption. Additionally, rectal solutions and suppositories along with intramuscular injection are also effective routes of administration. Subcutaneous use of these agents should be avoided due to their alkaline pH.

Barbiturate distribution, like that of all drugs, is dependent on the degree of lipid solubility of the compound, protein binding, and extent of ionization. Since barbiturates as a class reflect varying pharmaceutical and pharmacokinetic properties, three classes are used for categorization (Table 2). Peak concentrations of the ultrashort-acting barbiturates are seen within 30 s of injection. The ultrashort-acting barbiturates rapidly distribute into the CNS, exerting an effect which also dissipates rapidly. The longer-acting barbiturates such as phenobarbital have a slower onset of action with a prolonged duration of pharmacologic activity.

The majority of barbiturates are metabolized to inactive by-products by the liver, though the thiobarbiturates may also undergo minor metabolism by the kidney and brain. Mephobarbital and methabarbital undergo *N*-demethylation with the resultant formation of phenobarbital and barbital, respectively. Barbiturates can induce hepatic microsomal enzyme production which may result in the stimulation of metabolism of other pharmacologic agents.

While hepatic biotransformation is the main route of elimination of the barbiturates, most barbiturate analogues undergo some degree of renal excretion via glomerular filtration. Two such agents dependent upon this elimination pathway are barbital and phenobarbital. Tubular reabsorption of these agents decreases through alkalinization of the urine. This results in greater renal excretion of these agents, a property often exploited in the treatment of drug intoxication.

B. MANIFESTATIONS AND TREATMENT OF BARBITURATE INTOXICATION

The classic presentation of barbiturate intoxication is manifested by moderate to severe changes in the patient's level of consciousness.[20] In addition, respiratory depression and cardiovascular instability may also be prominent findings.[21] Hypotension, which is also a common finding in the intoxicated patient, is most likely due to increased vascular capacitance with resulting venous pooling. Both the central and peripheral effects of barbiturates can lead to hypoxia and a mixed acidosis.[22] Additional physical findings include miosis,[23] lack of pupillary light and corneal reflexes,[24] vertical gaze palsy,[25] flexor and extensor postures,[26] as well as abnormal temperature control.[27] While hypothermia is observed during the early phase of barbiturate intoxication, it is typically followed by hyperthermia in the later stages of intoxication.[27] Other findings may include self-mutilation (often violently)[28] and the development of the so-called "barbiturate blisters", lesions which in fact are nonspecific to barbiturate intoxication and appear only to represent pressure-induced skin lesions.[29]

The relationship between serum barbiturate concentrations, clinical symptomatology, and the ability to prognosticate a patient's clinical course remains very controversial.[20,30-32] Brain concentrations of the barbiturate analogues appear to demonstrate little, if any, relationship to serum concentrations of barbiturates. In general, a patient presenting with a serum concentration of ≥3 mg/dl for a short-acting barbiturate, ≥7 mg/dl for an intermediate-acting barbiturate, or ≥10 mg/dl for a long-acting barbiturate, and left untreated, is at greater risk of succumbing to the overdose.[30,31,33] However, these suggested relationships appear invalid in the presence of renal or hepatic disease or in cases of chronic barbiturate use or abuse.[20,31] Serum concentrations should not supersede the role of clinical assessment in determination of treatment following a toxic ingestion; rather, these should complement the treatment.

Evidence exists that the concurrent ingestion of ethanol with barbiturates may augment the toxic effects of these later agents. The mechanism proposed is a lowering of the "lethal dose" of drug through enhancement of barbiturate binding to brain receptors.[34] This belief, however, is controversial, since most patients with either a single barbiturate ingestion or an ingestion in combination with ethanol, who reach a treatment facility, survive the ingestion with an attendant low morbidity and mortality.[32,35,36] Overall, patients who ingest barbiturates and reach a treatment facility within a reasonable period of time often experience a favorable outcome.[32]

The use of syrup of ipecac in the conscious patient results in recovery of a greater amount of drug from the stomach than using gastric lavage. Ipecac syrup should be used with caution in the barbiturate-intoxicated patient as the competency of the patient's gag reflex cannot be assured. If induced emesis is not practical, gastric aspiration followed by gastric lavage with saline will be effective if performed within 4 h of ingestion.[37,38] Lavage should be performed following placement of a cuffed endotracheal tube to prevent aspiration of gastric contents into the lung.[37-39] Following gastric lavage, 1 g/kg of activated charcoal should be instilled, either in combination with sorbitol or followed within 30 min by a suitable cathartic such as 70% sorbitol (4 to 8 oz). Since the absorption of barbiturates occurs rapidly, drug removal and adsorption is **most** effective if performed within 1 h of ingestion.[40] In the overdose setting, however, drug absorption may be delayed, thus supporting the use of activated charcoal up to as long as 8 to 12 h postingestion. The use of smaller repeated doses of activated charcoal to increase drug elimination is effective for removal of phenobarbital from the blood, but to date, no clear-cut effect on patient outcome has been demonstrated.[41,42]

Forced diuresis with fluid loading and diuretics such as furosemide has been used for decades and can increase the elimination of phenobarbital by as much as 60%.[39,43] Effective diuresis should produce a urinary flow of 0.1 ml/min/kg.[39] There are little data to support the use of agents such as mannitol, acetazolamide, or dopamine.[44-46] While forced diuresis may increase the excretion of all barbiturates, it is most effective for phenobarbital. Forced diuresis should be avoided if the systolic blood pressure is markedly depressed.[47] Urinary alkalinization effectively augments the renal excretion of phenobarbital and barbital only.[48] Alkalinization of the urine is accomplished by the use of sodium bicarbonate (2 meq/kg) initially, followed by 2 to 4 meq/kg intravenously over 6 to 12 h to maintain urine pH above 7. Fluid therapy is important and should be considered early when hypotension is present. Fluid replacement with crystalloid should be used before the use of vasopressors such as norepinephrine or dopamine to maintain the systolic blood pressure and cardiac output.[49] Both pulmonary and cardiac function must be closely monitored during therapy. Analeptic agents such as doxapram hydrochloride have no place in the treatment of barbiturate poisoning.[39]

Hemodialysis and hemoperfusion can decrease the duration of coma caused by both short- and long-acting barbiturates.[50-53] However, since conservative treatment alone results in a mortality rate of less than 1%,[32,37] it would appear that dialysis should be used only in those cases where all other therapeutic measures fail or in patients with severe hepatic or renal disease.

Hypothermia may be treated by preventing further body heat loss; however, warming is necessary only if the body temperature is less than 30°C.[37] Other complications of barbiturate intoxication, including aspiration pneumonia and acute pulmonary edema, should be managed appropriately.

The outcome in the treatment of barbiturate intoxication is favorable if supportive therapy is instituted at a treatment center before respiratory depression can lead to CNS toxic effects. Fortunately, because of the decreased use of barbiturates for legitimate medical purposes, the incidence of barbiturate intoxication has decreased over recent years.

IV. TOXICITY WITH OTHER NONBARBITURATE SEDATIVE HYPNOTIC AGENTS

While benzodiazepines and barbiturates constitute the largest groups of available and clinically used sedative hypnotic agents, other nonbarbiturate agents are available for medical use. These agents include ethchlorvynol, glutethimide, and meprobamate. Methaqualone, a previously available nonbarbiturate hypnotic agent, is no longer available in many areas of the world, and thus we will not address this compound.

A. ETHCHLORVYNOL

This agent, a chlorinated alcohol, was first introduced in 1955 as a hypnotic agent. The drug has a rapid onset of action, with clinical effects being observed within 15 to 30 min after administration. Peak serum concentrations occur within 60 to 90 min following oral administration.[54] The drug is highly lipid soluble, accounting for a large volume of distribution and the attainment of high organ drug concentrations. This sequestration in organs most likely explains the biphasic pharmacokinetic pattern observed with the drug. Following oral administration, serum concentrations rise and fall rapidly over the first 7 to 14 h. Then, serum concentrations begin to rise, most likely due to movement of drug from tissues back into the intravascular compartment. Because of this phenomenon, half-life ranges of 10 to 25 h following therapeutic doses[54] and 21 to 105 h following toxic doses have been reported.[54,55] This proposed phenomenon may explain the long duration of coma seen after large ingestions (50 to 300+ h). Additionally, some investigations suggest that the elimination of ethchlorvynol may be dose dependent,[56] though this is difficult to ascertain from the available data.

Ethchlorvynol appears to undergo glucuronidation and/or hydroxylation, with a small portion being eliminated via the lungs.[54] It is unknown if the parent compound or its metabolite(s) is responsible for the pungent odor frequently noticed in intoxicated patients.[56]

The primary manifestations associated with ethchlorvynol toxicity include altered CNS status, dysarthria, mydriasis, nystagmus, areflexia, hypothermia, tachycardia, hypotension, ataxia, coma, and respiratory depression. Pulmonary edema, while more commonly seen after parenteral injection of the adulterated oral compound, is also reported after oral intoxication.[57] Serum ethchlorvynol concentrations do not appear to be useful as a prognostic variable.

Treatment of ethchlorvynol intoxication should include gastric decontamination and supportive therapy, usually in an intensive care unit. Methods to augment drug removal have been met with varying success.[58] Hemodialysis, peritoneal dialysis, and forced diuresis are of little benefit in augmenting drug removal from the body. Charcoal and resin hemoperfusion may remove up to 30% of the ingested dose and may result in improvement in the clinical status of the patient.[56] Due to the extensive tissue distribution of the drug, however, a rebound increase in ethchlorvynol serum concentration 4 to 6 h postdialysis may be observed, necessitating prolonged or repeated dialysis sessions.[56] Supportive therapy should be the rule unless the patient has ingested ≥100 mg/kg or has prolonged coma with life-threatening complications. In these severe cases, extracorporeal measures to assist in drug removal should be considered.

B. GLUTETHIMIDE

Glutethimide, first introduced in 1954, is structurally similar to methyprylon. While initially touted as a safe and effective barbiturate substitute, the potential for toxicity with this agent quickly became apparent.

Following oral administration of glutethimide, the drug is slowly and erratically absorbed.[4] Ethanol increases the absorption of this agent dramatically.[59] Due to its high lipid solubility, the drug rapidly concentrates in the brain and adipose tissue. Only a small amount of the drug is excreted in the urine (<2%), while the remainder of the drug is metabolized in the liver. While the average half-life is 5 to 22 h, half-lives averaging 40 h have been reported in intoxicated patients.[60] To complicate matters, glutethimide is a racemic mixture, the D- and L-isomers of which follow dissimilar metabolic pathways. The D-isomer undergoes hydrolysis of the glutarimide ring with the subsequent formation of 4-hydroxy-2 ethyl-2 phenyl glutarimide (4HG). This metabolite is conjugated with glucuronic acid or is excreted unchanged. The L-isomer also is hydrolyzed with release of acetaldehyde and then glucuronidated. Other metabolites of each isomer may exist, although complete metabolic conversion remains to be described. While initial data with single doses suggested that 4HG possessed no pharmacologic activity in humans, other data suggest a correlation between the degree of toxicity and the 4HG serum concentration.[60] To date, however, serum glutethimide and 4HG concentrations have found limited usefulness in directing the approach to the treatment of glutethimide intoxication.

Symptoms associated with glutethimide toxicity are similar to those observed with barbiturate intoxication, except for the occurrence of cyclic fluctuations in the depth of coma. Coma following flutethimide intoxication is usually prolonged and profound.[61-64] Acute apnea and convulsions, accompanied by signs of increased intercranial pressure, as well as persistent acidosis, hypotension, hypothermia, areflexia, pulmonary edema, and cardiac arrest, may be observed.[63] Dilated pupils (unilateral or bilateral) and urinary retention due to the anticholinergic properties of the drug may also be prominent signs of glutethimide intoxication. Persistent hyperthermia following a period of hypothermia may occur due to a "toxic fever" or due to the anticholinergic properties of the drug.[63]

Treatment of glutethimide overdose includes gastric decontamination via gastric lavage with a cuffed endotracheal tube in place. Since the onset of CNS depression occurs rapidly following drug ingestion, ipecac-induced emesis should be used only in patients whose mental status can be carefully monitored. Because the drug possesses marked anticholinergic properties, gastric lavage may be effective for up to 6 to 8 h after ingestion. There are little data to support the use of lipid lavage with castor oil in the treatment of glutethimide poisoning. Additionally, no data exist as to the efficacy of repeated doses of activated charcoal as a "GI dialysis" agent. However, given the nature of the metabolism and enterohepatic recirculation of glutethimide and its metabolites, repeated-dose charcoal may be of theoretical benefit and thus is recommended. Fluid therapy is also recommended in an attempt to promote thin and loose bronchial secretions considering the anticholinergic actions of the compound, though this remains controversial.[65] Furthermore, caution should be exercised due to the possibility of inducing pulmonary edema. Hypotension may be better treated with a combination of fluid and vasopressors.

Extracorporeal methods of drug removal have been successful in increasing drug clearance; however, the indications for use are limited. Peritoneal dialysis, hemodialysis, lipid hemodialysis, charcoal hemoperfusion, and resin hemoperfusion are effective in facilitating drug removal, with hemoperfusion being the most effective.[66-70] No clear guidelines exist as to when to use extracorporeal measures. Extracorporeal methods for drug removal may be used when serum concentrations exceed 3 mg/dl, in the presence of prolonged coma, in hypotension unresponsive to conventional therapy, as well as in progressive clinical deterioration despite adequate supportive therapy.[71] If employed, repeated prolonged hemoperfusion is often necessary due to the rebound increase in glutethimide concentration from tissue to serum.[71] Recent experience suggests that when one suspects glutethimide intoxication, one must consider the possibility of simultaneous codeine ingestion.[72] Ingestion of these two agents concurrently may result in increasing the toxicologic potential of each since codeine can decrease the concentration at which glutethimide is toxic by over 50%.

C. MEPROBAMATE

This agent was first synthesized in 1951 as a muscle relaxant, the sedative hypnotic properties of which were only later discovered. The absorption of meprobamate from the GI tract is rapid, with peak serum concentrations being observed within the first 3 h following ingestion. The elimination half-life is approximately 10 h. Meprobamate is 90% metabolized in the liver via hydroxylation and glucuronidation, while 10% is eliminated via the kidney.[4]

The primary manifestations of meprobamate intoxication include stupor, vomiting, paresthesia, seizures, coma, and hypotension.[73-75] Both tachycardia and bradycardia are also reported in meprobamate overdose.

The management of meprobamate intoxication includes drug removal through gastric lavage or induced emesis along with oral activated charcoal. Repeated-dose activated charcoal may decrease meprobamate half-life by approximately 50%. While hemodialysis or hemoperfusion has been successful in the treatment of meprobamate toxicity, these modalities are rarely needed unless supportive therapy alone appears unsuccessful.[75]

V. CONCLUSION

Benzodiazepines, barbiturates, and other nonbarbiturate sedative hypnotic agents possess the ability to induce serious morbidity and/or mortality when used indiscriminately. In younger children, exposure to these agents is usually accidental and requires supportive care in most instances for a successful outcome. In older children, adolescents, and adults, the abuse of these drugs for recreational purposes, along with their use in suicide attempts, represent a serious challenge to all health care providers.

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Chapter 12

THE ROLE OF DOXAPRAM IN CERTAIN PEDIATRIC CONDITIONS

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TABLE OF CONTENTS

I. Introduction 234

II. Pharmacological Actions 234
- A. Respiratory System 234
- B. Cardiovascular System 235

III. Therapeutic Uses 235
- A. Idiopathic Apnea of Prematurity 235
- B. Drug-Induced Respiratory Depression 236
- C. Congenital Central Hypoventilation Syndrome 236

IV. Pharmacokinetics 237

V. Adverse Effects 237

VI. Summary 238

References 238

I. INTRODUCTION

Doxapram was first introduced into the market as an analeptic with the capacity to stimulate respiration in 1962.[1] Subsequently, doxapram was proved to be beneficial as an adjunct in a variety of conditions requiring respiratory stimulation where complications may arise with the use of standard procedures such as mechanical ventilation or oxygen administration.[2] In reality, the role of doxapram was thus considered to be of minimal potential value in man.[3] However, in the last 5 years, interest has been regenerated in the use of doxapram in pediatric patients. In particular, doxapram appears to have found a role, albeit as an alternative or secondary agent, in the treatment of idiopathic apnea of prematurity resistant to methylated xanthines and congenital central hypoventilation syndrome.[4,5] It is evident that doxapram is not a first line of defense in the treatment of apnea of prematurity.[38] However, if one considers that approximately 65% of neonates develop apnea of prematurity,[6,7] it is conceivable that resistance to methylated xanthines could be greater than reported values and, hence, the usage of doxapram may be on the rise.

II. PHARMACOLOGICAL ACTIONS

A. RESPIRATORY SYSTEM

The primary mammalian response elicited by doxapram involves an alteration in respiration. It is generally accepted that in therapeutic concentrations doxapram is an effective and selective respiratory stimulant.[8] Regardless of the state of pulmonary function, be it normal or depressed, doxapram was found to stimulate respiration as evidenced by an increase in tidal volume. The ability to stimulate respiration under varying clinical conditions is summarized in Table 1. In patients with compromised lung function, a decrease in alveolar and arterial CO_2 tension accompanied the increase in tidal volume.[12,16,23] In contrast, doxapram enhanced the ventilatory response in normal subjects without a significant change in CO_2 tension.[9] It would appear that measurement of tidal volume is a more reliable index of doxapram-induced alterations in respiration.

Although it has been established that doxapram is a potent respiratory stimulant, a controversy exists as to the precise locus of action. With the use of cross-circulation and electrophysiological studies in dogs, doxapram-induced stimulation of respiration was found to be primarily due to direct activation of central, medullary respiratory centers.[24,25] A mild stimulation of the carotid chemoreceptors may also have contributed to the enhanced ventilatory response. In contrast, in decerebrate cats administered doxapram, the peripheral chemoreceptors were reported to exert a major influence in the respiratory response.[26,27] In humans, the marked elevation in the respiratory response to CO_2 was suggested to reflect a central action of doxapram.[9] However, in the presence of hypoxia, doxapram potentiated the ventilatory response to a greater extent than oxygen deficiency alone, indicating an action on the carotid body chemoreceptors.[9,12,28] Further, the ability of doxapram to potentiate the ventilatory response induced by aminophylline in apneic infants was suggested to be related to peripheral stimulation of respiration.[29] Both a central and peripheral component would thus appear to be involved in doxapram-stimulated respiration in children.[5,29,30]

The pharmacological action of doxapram on the respiratory system is selective. In a series of studies, Gupta and Dundee[19,31] demonstrated the ability of doxapram to block the respiratory depression induced by morphine without affecting the analgesia produced by the narcotic. In contrast, naloxone inhibited both the analgesia and the narcotic-induced respiratory depression. Further support for the view that the action of doxapram is selective was the observation that the dose required to produce convulsions was 10- to 38-fold higher than that needed to initiate increased ventilation in animals.[32] Other investigators[30,33] have reported that the convulsant to respiratory stimulant dose ratio for doxapram is 70:1. Evidence thus

TABLE 1
Doxapram-Induced Respiratory Stimulation in Various Clinical Conditions

Condition	Ref.
Normal	9
Chronic obstructive lung disease	2, 8, 10, 37
Congenital central hypoventilation syndrome	5
Obesity hypoventilation syndrome	11
Primary alveolar hypoventilation	12
Postoperative pulmonary complications	13, 14
Postanesthetic respiratory depression	15—17, 35, 39
Drug-induced respiratory insufficiency	18, 19, 34
Apnea of prematurity	4, 20, 56, 58
Neonatal respiratory depression secondary to maternal administration of narcotics during labor	21
Sleep hypoventilation	22
Ventilator-dependent brain damage	36

indicates that the pharmacological action of doxapram in eliciting respiratory stimulation is not only selective, but reflects a wide margin of safety.[29,32,41] The wide margin of safety noted for doxapram is in marked contrast to other analeptics.[30,32]

B. CARDIOVASCULAR SYSTEM

The cardiovascular system is also a target organ affected by doxapram. In doses which produce an increase in tidal volume, but not convulsions in the adult, doxapram was found to elevate blood pressure and heart rate.[2,12,16] The observed tachycardia and pressor effects were of short duration and modest in degree.[12,16] However, in a hypertensive individual, the pressor effect induced by doxapram was substantial.[2] Although cardiac irritability occurs frequently in patients with respiratory insufficiency,[40] it was suggested that the action on the cardiovascular system may precipitate arrhythmias.[3,38] Noe et al.[16] noted the presence of arrhythmias in 5 of 20 subjects administered doxapram, but this effect was not directly related to the action of the analeptic, as this response disappeared when doxapram was given a second time. A lack of effect of doxapram on cardiac rhythm has been reported by others in the adult.[2,12] It is of interest that in infants where cardiac function was monitored, doxapram did not produce any significant change in blood pressure or heart rate.[4,22,29] It would appear that in the therapeutic doses used thus far in pediatrics, doxapram does not seem to exert a major action on the cardiovascular system.

III. THERAPEUTIC USES

A. IDIOPATHIC APNEA OF PREMATURITY

The pathophysiology, incidence, and diagnosis of neonatal apnea has been extensively reviewed.[6] Apnea is defined as a respiratory pause of 20-s duration or longer and is believed to be the most troublesome respiratory problem in preterm infants. It has been postulated that brain damage may be associated with apnea in the neonatal period and indeed may predispose susceptible newborns to sudden infant death.[6] Although various causes can initiate apnea in 90% of premature infants at 28 to 29 weeks of gestation, the incidence of idiopathic apnea of prematurity is approximately 25%.[6,7] The initial pharmacological approach to the management of apnea of prematurity involves the use of methylated xanthines.[7,44,47] However, in infants refractory to methylated xanthines, the use of doxapram has proved effective

TABLE 2
Therapeutic Uses and Concentration of Doxapram in Infants[a]

Use	Concentration	Ref.
Idiopathic apnea of prematurity	2.5 mg/kg/h for 48 h	4, 20, 29
	2.5 mg/kg/h for 96 h	42
	1.0—1.5 mg/kg/h for 24 h	43
	0.5 mg/kg/h[b] for 24 h	57
Respiratory depression secondary to maternal narcotic use in labor	2—3 mg/kg	21
Congenital central hypoventilation syndrome	0.32 to 2 mg/kg/min for 10 min	5
	4 mg/kg/h for varying period up to 5 weeks	22

[a] In all cases doxapram was administered intravenously.

[b] If nonresponsive, increase by increments of 0.5 mg/kg/h for 24 h up to 2.5 mg/kg/h.

in the control of apnea of prematurity (Table 2). Since infants unresponsive to methylated xanthines require assisted aggressive mechanical ventilation, it was suggested that the use of doxapram would obviate the need for mechanical manipulation.[42,43] This latter factor may be important as mechanical manipulation facilities or staff are not always available.[4] Eyal et al.[29] also found that the addition of doxapram to the therapeutic regime in infants receiving aminophylline resulted in beneficial improvement of apnea in nonresponsive neonates. A synergistic response in this case may be due to the central action of aminophylline combined with the peripheral effect of doxapram. Further extensive study is needed to establish that doxapram is of benefit as an adjunct to methylated xanthines in the treatment of apnea of prematurity.

B. DRUG-INDUCED RESPIRATORY DEPRESSION

The use of narcotics in obstetrical analgesia is a highly specialized field and potentially dangerous to the fetus.[45] Despite the fact that pain is alleviated, the fetus is far more susceptible to the respiratory depression induced by maternal narcotic analgesic drug administration. In infants of mothers who received narcotic analgesics or general anesthetics during labor, respiratory depression occurred as evidenced by a fall in pH and a rise in the P_{CO_2} tension within 10 min after birth. With the administration of doxapram via the umbilical vein, Gupta and Moore[21] reported that the P_{CO_2} did not rise, while the pH fell less than that seen in control. Although doxapram proved effective in this one study,[21] the concensus is that in sedative-hypnotic poisoning, supportive mechanical therapy is the treatment of choice.[46] The fact that few reports exist on the use of doxapram in respiratory depression secondary to maternal narcotic analgesia during labor attests to the avoidance of analeptic administration to the fetus.

C. CONGENITAL CENTRAL HYPOVENTILATION SYNDROME

The incidence of Ondine's curse or congenital central hypoventilation syndrome is rare as well as poorly understood.[48] The condition is characterized in the infant by a marked depression of respiration primarily during quiet sleep,[48,49] although hypoventilation may occur during rapid eye movement sleep and when awake.[50] The central hypoventilation

TABLE 3
Doxapram-Induced Adverse Reactions in Infants

Effect	Ref.
GI hemorrhage, neuromuscular disturbances, hepatic dysfunction, and diaphoresis	5
No adverse effects	4, 21, 29
Jitteriness	42, 43
GI complications	22, 43
Vomiting, irritability, hyperglycemia	43

syndrome is believed to be associated with a lack of stimulation of medullary chemoreceptors.[48,51] Hunt et al.[5] demonstrated that doxapram administration to two infants with congenital central hypoventilation resulted in significant respiratory stimulation during quiet sleep. However, the lack of an improvement in response to CO_2 suggested that the site of doxapram action was on peripheral rather than medullary chemoreceptors. Regardless of the locus of action of doxapram, a drawback noted by Hunt et al.[5] was the neuromuscular manifestations of nonrespiratory medullary stimulation. In a subsequent study, Wessner and Boyle[22] found that enteral administration of doxapram to a child with congenital central hypoventilation also stimulated respiration, but did not produce neuromuscular abnormalities. It is evident that further study is necessary to establish a role for doxapram in the treatment of central congenital hypoventilation syndrome.

IV. PHARMACOKINETICS

The mode of doxapram administration is via the intravenous route. As a result of distribution and metabolism, doxapram disappears rapidly from the plasma.[52,53] Hepatic inactivation of doxapram is extremely rapid[52] such that a minimal amount is excreted unchanged.[53] Despite the rapid disappearance from plasma, Clements et al.[54] found that the plasma half-life was 6 to 7 h. Although pharmacokinetics were not studied, Moser et al.[2] demonstrated that doxapram infusion stimulated respiration for many hours. In infants with idiopathic apnea of prematurity unresponsive to methylated xanthines, the ability of doxapram to stimulate respiration lasted for 48 h after drug discontinuation.[29] It would appear that doxapram is more rapidly eliminated in infants as compared to adults.

V. ADVERSE EFFECTS

In adults, doxapram has been reported to produce hypothermia, salivation, lacrimation, tremors, jitteriness, hyperactivity, hypertension, tachycardia, arrhythmias, muscle rigidity, flushing, hallucinations, and frank psychosis.[2,3,38] However, the frequency of occurrence of adverse effects is controversial, ranging from common[38,55] to limited.[2,29] The adverse effects noted in infants are presented in Table 3. It should be mentioned that the adverse effects were dose-related and not observed in all patients in the study. In general, the incidence of side effects was low in infants, mild in nature, as well as reversible.[29] As the frequency of adverse effects was greater in very low-birth-weight infants, the margin of safety would appear to decrease in this population.[43] The appearance of side effects does not seem to be a limiting factor to the use of doxapram in pediatrics.

VI. SUMMARY

In certain clinical situations where infants are unresponsive to methylated xanthines and supportive therapy is not available, doxapram may serve as a temporary measure to alleviate apnea of prematurity. The beneficial usefulness of doxapram in the treatment of the rare disorder congenital central hypoventilation remains to be established. Doxapram is an effective respiratory stimulant with a wide margin of safety. At present doxapram is relegated to serve as an adjunct to other forms of therapy in pediatric patients.

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Chapter 13

METABOLISM AND TOXICITY OF ANTIPROSTAGLANDIN AGENTS

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TABLE OF CONTENTS

I. Introduction 242

II. Aspirin 242
  A. Mechanism of Action 242
  B. Toxicity Following Maternal Ingestion 242
    1. Neonatal Pharmacokinetics 242
    2. Coagulation Effects 242
    3. Laboratory Tests 243
  C. Breast Milk Excretion 243

III. Acetaminophen 243
  A. Mechanism of Action 243
  B. Toxicity Following Maternal Ingestion 244
  C. Toxicity Following Neonatal Ingestion 244
    1. Neonatal Pharmacokinetics 244
    2. Coagulation Effects 245
  D. Breast Milk Excretion 245

IV. Indomethacin 245
  A. Mechanism of Action 245
  B. Toxicity following Maternal Ingestion 245
    1. Primary Pulmonary Hypertension 245
  C. Toxicity Following Neonatal Administration 245
    1. Neonatal Pharmacokinetics 245
    2. Platelet Dysfunction 245
    3. Intraventricular Hemorrhage 246
    4. Renal Function Changes 246
    5. Plasma Glucose Changes 247
    6. Digoxin Toxicity 247
    7. Aminoglycoside Toxicity 247
  D. Breast Milk Excretion 247

References 247

I. INTRODUCTION

The main prostaglandin inhibitors to which neonates are exposed, either by transplacental passage, through breast milk, or by direct administration, are aspirin, indomethacin, and acetaminophen. Because of the popularity of aspirin as a nonnarcotic analgesic, many neonates are exposed to aspirin *in utero* which leads to subsequent difficulties during labor and delivery and toxicity during the neonatal period. Surveys done in the late 1960s and 1970s[1-3] reported that analgesics were among the most commonly ingested drugs during pregnancy and that greater than 60% of women surveyed utilized aspirin during some stage of their pregnancy. The use of acetaminophen during pregnancy has most likely increased with its increase in popularity in the general population; however, no surveys have specifically elucidated its use in pregnancy. The popularity of ibuprofen as an antipyretic and analgesic has also increased because of its over-the-counter (OTC) availability; however, there are no reports of neonatal adverse effects.

II. ASPIRIN

A. MECHANISM OF ACTION

Aspirin has been shown to irreversibly inhibit the conversion of arachidonic acid to prostaglandin G2 by acetylation of the enzyme prostaglandin synthetase (cyclooxygenase). This inhibition results in inactivation of the prostaglandin pathway and prevention of synthesis of all prostaglandins.[4] This knowledge lead to early trials evaluating the effectiveness of aspirin in the *in utero* treatment of patent ductus arteriosus[5] as well as to inhibit premature labor.[6] Aspirin taken at term has been reported to delay labor for 3 to 10 d.[7] Other anti-prostaglandin agents such as indomethacin have demonstrated better activity in the treatment of patent ductus arteriosus and are now exclusively used when pharmacologic therapy is indicated.

B. TOXICITY FOLLOWING MATERNAL INGESTION

1. Neonatal Pharmacokinetics

Aspirin readily crosses the placenta. Levy and Garrettson[8] studied four infants whose mothers had ingested 450 to 1300 mg of aspirin within 20 h of delivery. At delivery, blood samples were obtained from both the mother and the umbilical cord. In three of the neonates, plasma salicylate concentrations at birth were higher than respective maternal plasma salicylate concentrations. The ratio increased substantially with time. The results of pharmacokinetic analysis indicate that neonates metabolize aspirin in virtually the same way as adults (i.e., formation of salicyl phenolic glucuronide and conjugation with glycine). Garrettson et al.[9] indicate that neonates whose mothers have taken large doses of aspirin throughout pregnancy may be enzyme induced and may metabolize aspirin more rapidly than neonates who become acutely intoxicated. The half-life of aspirin in neonates appears to be much longer, and neonates also have a higher volume of distribution consistent with lower plasma protein binding. These principles were demonstrated by Lynd et al.[10] who reported a salicylate level of 31 mg/dl in a 36-h-old neonate. The maternal level at 36 h was 2 mg/dl.

2. Coagulation Effects

The implications of aspirin crossing the placenta with subsequent measurable neonatal serum levels are substantial. In addition to the possibility of actual salicylate intoxication,[10] decreased platelet function and diminished Factor XII (Hageman factor) activity have been noted. An *in vitro* study demonstrated that antenatal aspirin administration has more pronounced effects on the neonate's platelets than on maternal platelets.[11] These effects are more pronounced in the premature neonate. The mechanism by which aspirin decreases

TABLE 1
Summary of Adverse Effects Reported After Maternal Aspirin Ingestion in Neonates

Effect	Ref.
Decreased platelet function	13
Decreased Factor XII activity	13
Hemorrhagic phenomena	13
Intracranial hemorrhage	14, 15

platelet function is due to its ability to inhibit the release of endogenous adenosine diphosphate (ADP) which prevents platelet aggregation from occurring during hemostasis. The effect of aspirin on the platelet is "permanent" in that it lasts for the life of the platelet (4 to 7 d),[12] regardless of the elimination of aspirin. The defect is only corrected when new platelets are released from the bone marrow.

A total of 14 neonates whose mothers had taken aspirin during the week prior to delivery were compared to 17 neonates whose mothers had not taken aspirin.[13] In the neonates who were exposed to aspirin, decreased platelet function and Factor XII (Hageman factor) activity were noted (Table 1). These effects were seen in neonates with maternal ingestion as little as 650 mg of aspirin as long as 2 weeks prior to delivery. Hemorrhagic phenomena was noted at birth in 3 of 14 aspirin-exposed newborns. One newborn developed transient gastrointestinal (GI) bleeding, one developed cephalohematoma, and the third had bilateral periorbital purpura. Bleeding resolved spontaneously without residual morbidity in the three infants. In the same report, clinical bleeding was seen in only 1 of the 17 infants who was not previously exposed to aspirin. The child developed hemorrhagic conjunctivitis 2 d after silver nitrate instillation.

The effects of platelet dysfunction can be clinically significant, as demonstrated by Rumack et al.[14] An increased incidence of intracranial hemorrhage was seen in premature neonates whose mothers had ingested aspirin prior to delivery. Intracranial hemorrhage was also implicated as the cause of fetal death following congenital salicylate intoxication in one infant.[15] This effect can be particularly apparent in neonates who have an additional hemostatic defect such as hemophilia, von Willebrand's disease, or thrombocytopenia.[13]

3. Laboratory Tests

High serum aspirin levels have been reported to decrease the blood levels of serum chloride, total serum protein, calcium, cholesterol, uric acid, bilirubin, and thyroxine. Routine laboratory work in neonates who have been exposed to aspirin can be misleading.[16,17]

C. BREAST MILK EXCRETION

Low, intermittent doses of aspirin can be used safely by breast-feeding mothers. Reports have suggested breast milk levels ranging from 0.9 to 21% of a maternal dose can occur following aspirin administration.[18,19] Neonates should be monitored for abnormal platelet function if the mother has received large doses of aspirin.

III. ACETAMINOPHEN

A. MECHANISM OF ACTION

Like aspirin, acetaminophen has been reported to inhibit the enzyme prostaglandin synthetase (cyclooxygenase) *in vitro* (brain microsomal preparations).[20] This inhibition is thought to be the mechanism of the antipyretic and analgesic activity of acetaminophen.

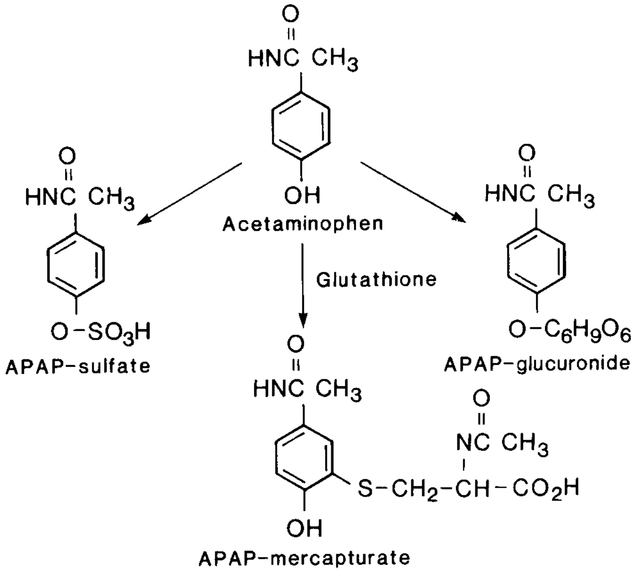

FIGURE 1. Metabolic pathways for acetaminophen.

There are also some data suggesting that acetaminophen inhibits prostaglandin synthetase in the renal medulla.[21] However, other *in vitro* studies have demonstrated that acetaminophen is not a good inhibitor of cyclooxygenase.[20] Some animal data suggest that acetaminophen has activity as potent as other prostaglandin synthetase inhibitors in closing the ductus arteriosus;[22-24] however, acetaminophen has not been used clinically for the treatment of patent ductus arteriosus.

B. TOXICITY FOLLOWING MATERNAL INGESTION

It appears that acetaminophen crosses the placenta. In a study of 112 pregnant women who were receiving oral *N*-acetylcysteine (NAC) treatment for acetaminophen overdose, follow-up data on 59 patients indicated 42 patients delivered infants with no documented neonatal abnormalities, and 9 of these 42 mothers had potentially hepatotoxic acetaminophen levels. One hepatotoxic mother (third trimester) delivered a 32-week stillborn fetus during the course of NAC treatment. Plasma acetaminophen levels in the abortus were 360 μg/ml. Massive hepatic necrosis was seen on autopsy. The 14 other women had either spontaneous or elective abortions in the first or second trimester.[25]

C. TOXICITY FOLLOWING NEONATAL INGESTION

1. Neonatal Pharmacokinetics

Unlike aspirin, the pharmacokinetics of acetaminophen differ in the neonate when compared with adults. As seen in Figure 1, there are three metabolic pathways for acetaminophen. It has been postulated that hepatocellular necrosis associated with acetaminophen overdose is due to the formation of a minor metabolite of the P450 mixed-function oxidase system.[26] In adults, the primary metabolic pathway is glucuronidation.[27,28] In neonates, the primary metabolic pathway is sulfation.[27,28] Levy et al.[28] indicated that of an orally administered dose of acetaminophen, in neonates 47.6% undergoes sulfation and 12.8% undergoes glucuronidation, with 2.4% being excreted unchanged. Following acute overdose of acetaminophen, it has been demonstrated that hepatic centralobular necrosis occurs when glutathione stores are depleted by 70%[26] and a larger amount of a toxic metabolite is formed. It is speculated that the increased dependence on sulfation as the metabolic pathway in neonates may protect them from hepatic necrosis following overdose.

2. Coagulation Effects

Unlike aspirin, acetaminophen in normal doses has not been demonstrated to affect platelet aggregation in normal patients or in those with hemophilia.[29,30] Following overdosage in adults, coagulation disturbances have been correlated with the severity of liver damage.[31,32] However, liver damage following acetaminophen overdose is unlikely in neonates because of the increased dependence on sulfation as previously discussed. Coagulation disorders would therefore be unlikely to occur.

D. BREAST MILK EXCRETION

Acetaminophen is considered safe for use in breast-feeding mothers. In studies, no acetaminophen or metabolites were found in the urine of nursing infants.[33,34]

IV. INDOMETHACIN

A. MECHANISM OF ACTION

Like the other agents previously discussed, indomethacin acts as an inhibitor of cyclooxygenase-mediated conversion of arachidonic acid to prostaglandin endoperoxides.[20]

B. TOXICITY FOLLOWING MATERNAL INGESTION

Maternal ingestion of indomethacin occurs infrequently. In the past, indomethacin was occasionally utilized both orally and rectally to inhibit premature labor.[35,36]

1. Primary Pulmonary Hypertension

Primary pulmonary hypertension characterized by inappropriately high pulmonary vascular resistance with subsequent right-to-left shunting of blood has been reported in two neonates whose mothers received indomethacin rectally (one case) and orally (two cases) to inhibit premature labor.[36] In both infants, the syndrome occurred within 12 h of maternal treatment. Symptoms resolved in both of these infants within 48 h.

C. TOXICITY FOLLOWING NEONATAL ADMINISTRATION

1. Neonatal Pharmacokinetics

The pharmacokinetics of indomethacin in neonates and premature infants can be described by a two-compartment open model[37] similar to that seen in adults. The large interindividual variability in elimination rate is due to variable gestational ages and hemodynamic situations. Indomethacin is cleared in the premature neonate 10 to 20 times more slowly than in adults.[38]

2. Platelet Dysfunction

Although indomethacin has been demonstrated to affect platelet aggregation in neonates due to an increase in bleeding time,[39] there are few reports of major hemorrhagic complications (Table 2). In the majority of reports of hemorrhagic complications, gastric perforation is described.[40,41] This, however, cannot be directly attributed to indomethacin, since gastric perforation occurs in newborns (two thirds of cases are in preterm infants), drug therapy notwithstanding.[42]

Decreased platelet function following single doses of indomethacin (0.2 to 0.3 mg/kg by nasogastric tube) occurred in two premature infants.[43] In both cases, platelet aggregation studies revealed no aggregation in response to either 5.0 μM ADP or collagen for 2 to 4 d following indomethacin administration. In one neonate, 85% aggregation was seen in response to 5.0 mmol of ADP 10 d after indomethacin administration. One neonate developed GI bleeding on the day following indomethacin administration; the other had no apparent clinical effect from the decreased platelet aggregation.

TABLE 2
Summary of Adverse Effects Reported After Neonatal Indomethacin Administration

Effect	Ref.
Platelet dysfunction	39, 43
GI tract hemorrhage	44
Renal function changes	51—55
Decreased plasma glucose	60, 61
Enhanced digoxin toxicity	62, 63
Enhanced aminoglycoside toxicity	64

In a subsequent report,[39] an increased bleeding time was seen in 25 consecutive preterm infants who received three doses of indomethacin for ductal closure. Within 2 h after the first indomethacin dose, there was a prolongation of bleeding times from 3.6 ± 1.0 to 8.7 ± 2.5 min (p <0.0001). No significant increase beyond this level was seen at the end of the 3-d course. Bleeding times were still elevated 48 h after the last dose of indomethacin, and 6 of the 25 infants had clinical evidence of bleeding after indomethacin administration. In five infants this was manifested as transient occult hematuria. One infant had occult blood in his stool and scant bleeding from the endotrachial tube.

Chirico et al.[44] report a case of massive GI tract hemorrhage within 20 h after administration of indomethacin, 0.2 mg/kg i.v., as a single dose to a 7-d-old infant girl who had no previously clinical signs of bleeding and normal coagulation studies (prothrombin time, 15.3 s; control, 14.7 s; fibrinogen, 199 mg/dl; platelets, 268,000 per cubic millimeter). This was accompanied by a fall in hematocrit to 21% and a depletion of coagulation factors. Volume exchange transfusion through the umbilical vein using donor blood resulted in dramatic improvement in the infant's clinical condition.

3. Intraventricular Hemorrhage

No association between indomethacin therapy and causation or extension of intraventricular hemorrhage has been demonstrated.[39,45-50]

4. Renal Function Changes

Following indomethacin therapy, oliguria, decreased glomerular filtration rate, reduced sodium water excretion, increased serum creatinine, and a decrease in urinary excretion of prostaglandin E have been described.[51-53] In a prospective study,[54] 17 premature neonates received three doses of indomethacin, 0.2 mg/kg i.v., at 12-h intervals. Renal function variables were measured before and at 24 and 48 h. Serum sodium showed no significant fluctuation. Serum osmolality decreased significantly in the first 24 h, but had almost returned to pretreatment values by 48 h. The glomerular filtration rate (as measured by creatinine clearance) decreased 30% during the first 24 h and returned to normal at 48 h. Urine sodium excretion decreased by 30% (p <0.01) in the first 24 h, rebounded, but remained lower than pretreatment values at 48 h. Fractional excretion of sodium also decreased as did urinary flow rate (18%). The urine flow rate returned to pretreatment levels 24 h after cessation of therapy.

In contrast to the results of John et al.,[54] other studies[48,51,55] demonstrated mild hyponatremia following indomethacin therapy. One report[56] described five low-birth-weight neonates who demonstrated clinically significant hyponatremia (less than 130 mg/dl within 48 h of receiving indomethacin). The reasons for this discrepancy may be due to a difference in fluid intake in the neonates while receiving indomethacin[54] or, as suggested by Hammerman et al.,[56] hyponatremia may be more pronounced in low-birth-weight neonates (less than 1100 g) and those seriously ill with other major complications.

Simultaneous administration of furosemide has been suggested to prevent the renal effects of indomethacin without affecting the efficacy of the drug for treating patent ductus arteriosus.[52] A total of 19 premature infants were randomized to receive either indomethacin alone (0.3 mg/kg i.v.) (9 infants) or indomethacin (0.3 mg/kg i.v.) and furosemide (1 mg/kg i.v.) (10 infants). Renal function tests were performed in both groups following the first indomethacin dose. Neonates who received indomethacin alone had significantly lower urine output, fractional excretion of sodium and chloride, and glomerular filtration rates at 0 to 12 h when compared to neonates who had received both drugs. Urine output and fractional excretion of chloride continued to decrease at 12 to 24 h in the indomethacin group.[52] The beneficial effects of furosemide may be due in part to the ability of furosemide to increase prostaglandin E excretion in the urine.[43] It is postulated that indomethacin affects water excretion by changing renal hemodynamics[57,58] and potentiating the action of vasopressin.[59]

5. Plasma Glucose Changes

A significant fall (up to 40%) in plasma glucose can occur following indomethacin administration.[60,61] Six infants demonstrated a fall in plasma glucose at 1, 6, 12, and 24 h following a 0.3-mg/kg i.v. dose.[61] No significant change in insulin levels was seen. The lowest plasma glucose levels were seen within 6 h of indomethacin administration. No clinical signs of hypoglycemia were manifested.

6. Digoxin Toxicity

Digoxin is commonly administered concomitantly with indomethacin for the treatment of patent ductus arteriosus. Increased serum concentrations of digoxin occurred in 11 neonates when indomethacin was added to therapy. Serum digoxin concentration increased from 2.2 ± 0.7 to 3.2 ± 0.7 ng/ml ($p < 0.001$) and was correlated with decreased urine output following indomethacin.[62] A similar case report was reported by Schimmel et al.[63]

7. Aminoglycoside Toxicity

Increased aminoglycoside levels can occur following concomitant administration of indomethacin and aminoglycosides due to the ability of indomethacin to decrease urine output.[64]

D. BREAST MILK EXCRETION

The American Academy of Pediatrics[33] recommends that indomethacin can be safely administered during the breast-feeding period. There has been one report of seizures in a neonate whose mother was receiving indomethacin in doses of up to 3 mg/kg. No other cause of the seizures was found.[65]

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Chapter 14

PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS ASSOCIATED WITH H_1 RECEPTOR ANTAGONISTS

S. Kacew

TABLE OF CONTENTS

I. Introduction 252

II. Chemistry 252

III. Pharmacological Actions 252

IV. Therapeutic Uses 253
  A. Allergic Disorders 253
  B. Vomiting and Pregnancy 253
  C. Asthma 255
  D. Otitis Media 255
  E. Common Cold 256

V. Pharmacokinetics 256
  A. Chlorpheniramine 256
  B. Diphenhydramine 256
  C. Hydroxyzine 257
  D. Other Antihistamines 257

VI. Adverse Effects 258

VII. Summary 258

References 260

I. INTRODUCTION

The autocoid histamine is responsible for a variety of effects in the mammal. In general contracture of the smooth muscle of gut and bronchi as well as relaxation of blood vasculature is believed to be mediated by H_1 receptors.[1,2] The secretion of gastric acid is mediated via the activation of H_2 receptors.[1,3] One of the modes of classification of these receptors has been the manner in which certain drugs antagonize either H_1 or H_2 receptor populations. In discussion of drug usage in pediatric gastroenterology, the pharmacologic properties of H_2 receptor antagonists such as cimetidine and ranitidine are described. In this chapter, the term antihistaminic drug will be synonymous with H_1 receptor antagonist.

From a historical perspective, the H_1 receptor antagonists have been in the pharmaceutical market since the 1940s.[1,32] Estimates of the usage of these compounds reveal that in 1950 approximately $100 million was spent to purchase these agents,[4] while in 1966 approximately 12 to 75 million prescriptions were filled for antihistaminic drugs.[5] This latter value does not include the fact that antihistaminic agents are also sold without prescription or that these compounds are present in combination with other formulations as part of a ''cold'' remedy or as sleeping aids. The easy accessibility to these drugs, especially as ''over-the-counter'' agents, has resulted in reports of toxicity and death. However, it should be emphasized that despite the excessive use of antihistaminic agents, these drugs are relatively nontoxic in usual doses. The aim of this chapter is to review the adverse effects of antihistaminic agents in light of recent reports associated with dermal exposure.

II. CHEMISTRY

Although the antihistaminics share a similar mechanism of action, structural differences exist between these agents. The drugs to be discussed and the chemical classification are provided in Table 1. The drugs shown in Table 1 are currently available and have been reported to produce adverse effects in children. Other antihistaminic drugs also produce toxicity, but have been removed from the druggists' shelves. Examples of these latter drugs include methapyrilene, pyranisamine, and prophenpyridamine.[6] This list of antihistaminics is far from the total number of drugs available; however, the agents described include those for which data are available on the affects in children.

III. PHARMACOLOGICAL ACTIONS

The antihistaminic agents inhibit the actions of histamine at the H_1 receptor in a reversible competitive fashion.[21] In general, blockers of the H_1 receptor are known to antagonize the constrictor action of histamine on respiratory and GI smooth muscle.[1,32] Similarly, histamine-induced increase in capillary permeability as well as formation of edema and wheal is effectively blocked by H_1 blockers. The histamine-induced vasoconstriction in the vasculature is completely blocked, while the vasodilation component is only partially affected by antihistaminics. The H_1 blockers also exert pharmacological actions unrelated to the H_1 receptor. One of the prominent systems affected by antihistaminics is the central nervous system (CNS) where stimulation or depression can arise. Usually therapeutic doses produce a sedative effect, although excitation has been reported at ordinary dosages. In general stimulation of the CNS is associated with poisoning by H_1 blockers. The prevention of motion sickness by antihistaminics is believed to be related to a central action. H_1 blockers are known to antagonize the effects of acetylcholine at the muscarinic receptors. Finally, antihistaminic drugs are effective in blockade of sodium channels in excitable membranes, resulting in a local anesthetic action.

TABLE 1
Classification of Commonly Encountered Antihistaminic Preparations in Pediatrics

Class	Generic	Trade name
Ethanolamines	Diphenhydramine	Benadryl®
	Dimenhydrinate	Dramamine®
	Carbinoxamine	Clistin®
	Doxylamine	Decapryn®
Ethylenediamines	Tripelennamine	PBZ®
	Pyrilamine	Neo-Antergan®
Alkylamines	Chlorpheniramine	Chlortrimeton®
	Brompheniramine	Dimetane®
	Triprolidine	Actidil®
Piperazines	Hydroxyzine	Atarax®
Phenothiazines	Promethazine	Phenergan®
Piperidine	Cyproheptadine	Periactin®

IV. THERAPEUTIC USES

It is not within the scope of this chapter to include all the therapeutic uses for which antihistaminic drugs are prescribed in adults. Further, self-medication for colds at any age or as a sleeping aid in adults is a known practice, but is not necessarily of therapeutic benefit. The reported uses of antihistaminic agents in children are listed in Table 2. It is evident that the prescribed use of these agents in pediatrics is related to the pharmacological actions at the H_1 receptor. It should also be mentioned that H_1 antagonists are utilized by themselves in certain conditions such as allergic skin diseases.[32] However, these compounds are also used as adjuncts in anaphylaxis,[32] asthma,[35-37] or otitis media.[38] In the subsequent discussion, the controversial use of H_1 blockers as adjunctive therapy will be described.

A. ALLERGIC DISORDERS

Although antihistaminic agents share a common mechanism of action, the efficacy in treatment of atopic dermatitis in children differs between these drugs. In 20 children with pruritis associated with atopic dermatitis, Klein and Gallant[13] demonstrated that hydroxyzine provided significantly greater relief of pruritis as compared to cyproheptadine. Similarly, Baraf[16] found that hydroxyzine was more effective than cyproheptadine in the treatment of chronic urticaria, contact dermatitis, and allergic dermatitis in adults. This was further verified experimentally where hydroxyzine was found to produce greater inhibition than cyproheptadine in histamine or allergen-induced skin wheal and flare reaction.[17,18] It is of interest that hydroxyzine was also more effective than other H_1 blockers, including diphenhydramine, chlorpheniramine, promethazine, and tripelennamine, in suppression of histamine-induced itching and antagonism of allergic skin test, as well as blockade of dermographism.[18,25,26] In contrast, in cold-induced urticaria, chlorpheniramine proved less effective than cyproheptadine in alleviation of the symptoms.[27] At present, it is not known whether hydroxyzine is more effective than cyproheptadine in suppression of the condition of primary acquired cold urticaria.

In the treatment of allergic disorders in adults, a combination of H_1 antagonists with H_2 blockers (e.g., cimetidine) has been administered. A combination of cimetidine with promethazine proved more effective than either agent alone in the treatment of atopic dermatitis.[28] In the condition of chronic urticaria, the combination of cimetidine with hydroxyzine was the most effective therapeutic regime as judged by the patient subjectively and suppression of wheal response.[29,30] On a comparative basis, cimetidine combined with cyproheptadine or chlorpheniramine was found by Harvey et al.[29] not to be as effective as hydroxyzine.

TABLE 2
Therapeutic Uses of Antihistaminic Drugs in Children

Abnormality	Drugs used	Ref.
Allergic rhinitis	Chlorpheniramine	7, 8, 24
	Diphenhydramine	19, 24
	Hydroxyzine	39
	Triprolidine	40, 41
	Azatidine	42
	Tripelennamine	11, 24
	Brompheniramine	24, 32
	Pyrilamine	24
	Terfenadine	101, 102
Eosinophilic nonallergic rhinitis	Pyrilamine	24
Atopic dermatitis	Hydroxyzine	13, 19, 20, 23, 32
	Promethazine	14, 28
	Cyproheptadine	13, 16, 32
Idiopathic urticaria	Hydroxyzine	29, 30
	Chlorpheniramine	29—31
	Cyproheptadine	29, 30
Primary acquired cold urticaria	Cyproheptadine	27
Dermographism	Hydroxyzine	19, 25
Varicella	Diphenhydramine	9
Anaphylaxis	Hydroxyzine	32
	Diphenhydramine	32
Vomiting	Promethazine	15, 19
	Dimenhydrinate	15
	Cyclizine	19
Irritability	Diphenhydramine	10
Asthma	Diphenhydramine	43
	Chlorpheniramine	35
	Hydroxyzine	37, 44
Otitis media	Triprolidine	45
	Brompheniramine	38
	Chlorpheniramine	46, 47

In agreement with this finding was the report by Commens and Greaves,[31] who demonstrated that cimetidine plus chlorpeniramine failed to provide any significant advantage over the H_1 blocker alone in the treatment of idiopathic urticaria. At present, the therapeutic efficacy of combination H_1 and H_2 antagonists remains to be studied in children. The H_1 antagonists are metabolized by the liver and are eliminated more rapidly in children[8,12] compared to adults.[33] Further, it has been established that cimetidine inhibits hepatic microsomal enzymes.[34] Thus, it is conceivable that the combination of cimetidine with a H_1 blocker would increase the half-life of the H_1 antagonist and potentially create a greater risk for adverse reactions in the pediatric patient.

B. VOMITING AND PREGNANCY

The use of antihistaminic agents to control nausea and vomiting in the first trimester of pregnancy is mentioned briefly. The reports of teratogenic effects of antihistamines, in particular Bendectin®, are controversial and have not been clearly demonstrated. However, this has resulted in the removal of these agents from the market.[22] It is generally acknowledged that morning sickness is self-limiting[15] and that antihistaminics should be avoided in the first trimester of pregnancy.[1]

In patients in labor, the symptoms of fear and anxiety have been controlled with the use of drugs by some physicians. Bare[88] demonstrated that the addition of hydroxyzine to meperidine potentiated the latter compound with respect to sedation and analgesia when administered during labor. The newborn was not affected as determined by Apgar, but this drug combination proved important in reducing the amount of narcotic necessary. Similarly, Benson and Benson[89] employed hydroxyzine and meperidine for obstetric analgesia and reported that this combination was safe, effective, and acceptable when administered within 1 h of delivery. The Apgar ratings of all neonates receiving this drug regimen were similar to placebo-born infants. However, the use of antihistaminics, especially the piperazine or phenothiazine type, is not recommended in early pregnancy as teratogenic effects are known to occur in animals.[90-92] In addition, Prenner[93] demonstrated that in pregnant women administered hydroxyzine to control severe eczema throughout gestation, there was a resultant jitteriness, tachypnea, irritability, clonic movements, and shrill cry in the infant. All these symptoms resembled an early neonatal withdrawal syndrome.[94] It is thus evident that high doses of hydroxyzine *in utero* may induce withdrawal symptoms and provide support for the avoidance of antihistamine use in pregnancy.

C. ASTHMA

Based on early data in which controlled clinical trials were not conducted, reports appeared that antihistamines might exert a deleterious effect on the clinical course of asthma.[43] With a clearer understanding of the mechanisms involved in the initiation of asthmatic attacks, it became evident that the use of antihistaminics alone for the treatment of asthma is questionable.[50] On the one hand, chlorpheniramine was found to dilate the bronchi,[51] inhibit histamine-induced bronchospasm,[35,36] and partially prevent exercise-induced asthma.[52] Despite the fact that hydroxyzine alone hastened recovery in exercise-induced asthma, Bierman et al.[44] demonstrated that theophylline was significantly more effective. Further, well-designed studies have demonstrated that H_1 antagonists such as chlorpheniramine, diphenhydramine, promethazine, or hydroxyzine do not markedly improve pulmonary function in asthmatic children.[19,37] The concensus among physicians at present is that H_1 antagonists on their own are not of therapeutic benefit in the treatment of asthma.[32]

The finding that antihistaminic drugs did not exacerbate asthmatic symptoms suggested that these drugs could play a role as adjuncts in the treatment of allergic rhinitis or urticaria in children with asthma.[19] This is supported by the observation that hydroxyzine in combination with theophylline proved superior to the methylated xanthine in alleviation of the symptoms of exercise-induced asthma.[44] In the treatment of bronchial asthma, Brandon[37] found that addition of hydroxyzine to pirbuterol was beneficial not in the enhancement of bronchodilation, but in the reduction of adverse effects due to pirbuterol. This latter phenomenon enabled the asthmatic patient to continue the course of therapy. These findings are in contrast to the report that antihistamines produce bronchoconstriction and, consequently, could prove detrimental to an asthmatic individual.[53] It is evident that in the presence of allergic disorders a child suffering from asthma can be administered an antihistamine without fear of exacerbating the asthmatic attack.[19,32] In exercise-induced asthma, antihistaminic agents in combination with a bronchodilator appear to be more beneficial to the patient than either drug alone.[37,44]

D. OTITIS MEDIA

The usefulness of antihistamines in the treatment of otitis media is controversial and dependent on the stage of the disease. In acute otitis media, the use of chlorpheniramine in combination with an antibiotic proved beneficial, shortening the duration of nasal congestion and preventing middle ear effusion from occurring.[46,48] In contrast, Randall and Hendley[38] found that the incidence of acute otitis media was not diminished in the presence of brompheniramine. In the case of otitis media with effusion, which is synonymous with serious or secretory otitis media, chlorpheniramine or brompheniramine was not effective in reducing the effusion.[45,47,49] It would appear that antihistamine use in serious otitis media is not of benefit to the child, while in the acute form of this disease, the beneficial efficacy remains to be demonstrated.

E. COMMON COLD

Antihistamines administered alone or in combination with other agents have been promoted as effective agents in combating symptoms associated with the common cold. However, in well-designed studies, West et al.[54] demonstrated that antihistamines are not effective in counteracting the symptoms seen in the common cold. Indeed, ingestion of antihistamines results in sedation, and patients taking the drug for a cold have fallen asleep while operating machinery or driving an automobile. West et al.[54] warned against the indiscriminant use of antihistamines for treatment of colds in view of the potential risks. Despite the scientific agreement that the role of antihistamines in the symptomatic treatment of the common cold remains controversial and unsubstantiated, Howard et al.[55] demonstrated the superiority of chlorpheniramine over placebo in lessening the degree of the symptoms of the common cold. However, the selection of patient and experimental design was restrictive such that one could not apply the rules to the general populace who are ingesting the antihistaminic agent. At present, there is no clear-cut evidence that antihistaminic drugs are of therapeutic value for the symptomatic treatment of colds in children.

V. PHARMACOKINETICS

A. CHLORPHENIRAMINE

In light of the widespread and indiscriminant use of antihistaminic drugs, it is surprising that relatively few studies are available on the pharmacokinetics of these agents in children. In 1981, Thompson et al.[7,58] were the first to describe the pharmacokinetic characteristics of chlorpheniramine administered intravenously to children. The half-life was found to be approximatley 9.6 h, which is considerably shorter than that reported for the adult.[33,56,59] In a subsequent study, Simons et al.[61] found that the half-life of chlorpheniramine was prolonged in children in comparison to adults[56,57] following oral drug administration. Although the biologic half-life of chlorpheniramine is shorter in the child, the clearance rate or elimination half-life was either similar[59] or shorter[33,57] in the adult. It is of interest that Simons et al.[8,32] reported that the volume of distribution of chlorpheniramine was larger than any physiologic volume and this was indicative of extensive tissue binding. In support of this view is the finding by Peets et al.[60] that over 70% of chlorpheniramine was bound to serum protein in adults. A further factor affecting bioavailability is the extensive metabolism of chlorpheniramine with only 11% excreted unchanged.[60,61] Despite the low degree of bioavailability, serum concentrations of chlorpheniramine ranging from 2.3 to 12.1 ng/ml suppressed signs and symptoms of allergic rhinitis in children for 30 h after drug administration.[8] Evidence thus suggests that tissue binding plays a critical role in chlorpheniramine action and that the usual practice of drug administration (three to four times daily) is not warranted in the child.[61]

B. DIPHENHYDRAMINE

Diphenhydramine has been widely used since 1946 in the treatment of allergic disorders and as a sedative.[10] Although the pharmacokinetics have not been established in children, the pharmacological effects are rapid in onset and short in duration.[6,11] These pharmacokinetic properties are probably related to a rapid absorption as well as extensive hepatic drug degradation in children. In agreement with this hypothesis was the finding that 64% of diphenhydramine appeared as metabolites over a 24-h duration in adults.[62] While Glazko et al.[62] reported a biological half-life of 7 h, Carruthers et al.[63] found a shorter half-life of 3 to 4 h. In addition to measurement of the clearance rate, it was established that the antihistaminic effect persisted for 7 h while sedation was only noted for 3 h. Carruthers et al.[63]

suggested that individuals may be more susceptible to the antihistaminic effect of diphenhydramine. Whether differences in pharmacological responses occur in children has not been reported, but it would be of benefit to suppress allergic manifestations without initiating sedation.

C. HYDROXYZINE

Despite the fact that hydroxyzine is the antihistamine of choice for the treatment of allergic skin disorders,[13,16] virtually little is known about the pharmacokinetics of this drug in children. Following the oral administration of hydroxyzine to 12 children, Simons et al.[12] found a biological half-life of 7 h with a peak serum concentration reached in 2 h. Although the peak serum level was attained at 2 h, the pruritis was significantly suppressed for 12 hours. In comparison, a half-life of 20 h and a markedly slower clearance rate for hydroxyzine was noted in seven adults.[64] Consequently, the hydroxyzine-induced suppression of wheal persisted for 60 h. The finding that the biological half-life of hydroxyzine is shorter in the child as compared to the adult is similar to that reported for chlorpheniramine.[7,8] However, Fouda et al.[65] found that the half-life of hydroxyzine in adults was as short as 3 h. It was suggested that the discrepancy in the latter study might be due to sampling time as serum concentrations were only measured quantitatively up to 8 h. Regardless of the discrepancy in half-life, it is clearly evident that the ability of hydroxyzine to suppress allergic manifestations exceeds the period at which peak serum levels are seen.

Absorption of hydroxyzine from the GI tract is rapid[65] and complete as less than 2% of an administered dose is recovered unchanged in feces and urine.[66] As in the case of other antihistaminics, hydroxyzine is extensively metabolized.[12,66] At present, the tissue distribution and pharmacokinetics of a multiple-dose regimen of hydroxyzine remain to be established.

A phenomenon which has thus far received little attention but may play a role in chronic drug therapy is tolerance. Chronic administration of hydroxyzine to patients with allergic rhinitis failed to increase the incidence of side effects as drug duration was prolonged.[73,74] However, these individuals were capable of tolerating larger hydroxyzine doses or a higher frequency of drug administration. The tolerance factor has not been examined in children, but would be of importance, especially in infants requiring a chronic drug regimen. It is of interest that tolerance to triprolidine to the CNS effects including mental performance, reaction time, and sedation, has already been reported in adults.[75]

D. OTHER ANTIHISTAMINES

Pharmacokinetic data are not currently available in children for antihistaminic drugs in this group despite the fact that these compounds are prescribed for children.[67] In the adult, brompheniramine was found to reach mean peak serum levels in 3 h and to possess a half-life of 24 h.[68] Significant suppression of allergic manifestations was observed 48 h after drug administration. As in the case of other antihistamines, 95% of an administered brompheniramine dose was metabolized in man.[69] Based on existing pharmacokinetic data, Simons et al.[68] suggested that the frequency of brompheniramine dosing may be excessive in children.

Finally, with respect to pharmacokinetics, administration of triprolidine was found to possess a biological half-life of approximately 5 h.[70,71] Triprolidine was detected as early as 30 min after ingestion and attained a peak serum level after 2 h. However, the ability to suppress allergic manifestations was still persistent after 24 h.[72] Triprolidine is extensively metabolized by the liver with the metabolites being excreted in urine. It would appear that the efficacy of triprolidine outlasts the mean peak serum concentration, a common characteristic of antihistaminic drugs.

TABLE 3
Reported Adverse CNS Effects Attributed to Antihistamines in Children

Reaction 1	Reaction 2	Reaction 3	Reaction 4
Stimulation	Depression	Neuropsychiatric	Miscellaneous
Insomnia	Drowsiness	Nightmares	Dizziness
Nervousness	Somnolence	Impaired judgment	Headache
Vagal stimulation	Narcolepsy	Delusions	Syncope
Tachycardia and hypertension	Weakness	Hallucinations	Fever
	Ataxia	Mental depressions	Hyperthermia
Muscular twitchings	Delirium	Reduced mental efficiency	Cerebral edema
			Electroencephalographic changes
Hyperreflexia	Coma	Confusion	
Tremor		Toxic psychosis	
Convulsions		Akinetic seizures	
Irritability			
Hyperactivity			
Aphasia			
Hyperpyrexia			

Adapted from References 6, 11, 76, and 77.

VI. ADVERSE EFFECTS

The adverse effects attributed to antihistamine drug use have been documented since the 1950s. The CNS adverse effects as listed in Table 3 have appeared in several reviews.[6,11,76,97,98] In addition to the CNS, other mammalian organ systems are affected by antihistamines as illustrated in Table 4. It has been estimated that 10 to 63% of individuals experience some side effects when taking antihistamines.[84] However, the incidence of fatalities is less than 1%.[6]

An important feature associated with severe antihistamine intoxication and death is the route of administration. Clearly, the most common and well-established route of antihistamine intoxication is via oral ingestion (Table 5). Although an isolated report, Schipior[80] reported the presence of hallucinations, seizure activity, and blurred vision in a child whose skin was sprayed with an antihistamine for poison ivy. The subsequent danger associated with dermal antihistamine absorption and toxicity was borne out by Filloux[9] and Shawn and McGuigan.[14] It should be mentioned that the onset of symptoms takes longer following dermal application as compared to the oral route. It is evident that in susceptible children the dermal application of creams containing antihistamines could initiate serious adverse reactions.

The management and treatment of antihistamine intoxication is symptomatic and supportive.[10,14] In the case of oral ingestion, gastric lavage is utilized,[10,32] while the skin is cleansed to remove any unabsorbed drug in cases of dermal intoxication.[14] Other measures include termination of convulsions with diphenylhydantoin and assisted ventilation for cardiorespiratory depression. In conditions where the pediatric patients fail to respond to symptomatic and supportive therapy, physostigmine has proved effective in alleviation of seizures, tachycardia, and hallucinations.[83,85,86] However, routine use of physostigmine is not recommended in antihistamine intoxication as the anticholinesterase itself produces undesirable effects.[87]

VII. SUMMARY

The antihistamines are of therapeutic value in specific pediatric disorders. It is inappropriate, self-administration which constitutes a potential danger. Dermal as well as oral

TABLE 4
Reported Antihistamine-Induced Adverse Effects on Other Systems

System	Effects	Ref.[6,11,76,77]
Peripheral nervous system	Toxic neuritis	
	Paresthesia	
	Paralysis	
	Areflexia	
Special	Tinnitis	
	Vertigo	
	Labyrinthitis	
	Dilated pupils	
	Blurring of vision	
	Facial dyskinesia[a]	78, 79
	Visual hallucinations[a]	9, 14, 80
	Subsensitivity	99, 100
GI system	Anorexia, nausea, and vomiting	
	Heartburn	
	Cardiospasm	
	Diarrhea	
	Constipation	
Cardiovascular system	Hypotension	
	Vasovagal phenomena	
	Syncope	
	Shock-like state	
	Palpitation	
	Tachycardia	
	Hypertension	
	Cerebral edema	
	Electrocardiographic changes	
	Cardiovascular collapse[a]	10, 81
	Cerebral dysrhythmia[a]	82
Genitourinary system	Irritative symptoms	
	Spasmogenic retention	
	Upper nephron nephrosis	
Hematological system	Neutropenia	
	Agranulocytosis	
	Hemolytic anemia	
Skin and mucous membranes	Dry mouth	
	Dermatitis	
	Urticaria	
	Flushed skin[a]	83

[a] Denotes symptoms reported but which are not listed in References 6, 11, 76, and 77.

TABLE 5
Relation Between Route of Administration and Antihistamine Intoxication in Children

Route	Response	Ref.
Oral	Severe intoxication	6, 10, 11, 76, 77, 82, 83
	Death	6, 11, 76, 81, 95, 96
Inhalation plus percutaneous	Severe CNS toxicity	80
Dermal	Severe CNS toxicity	9, 14

route absorption of antihistamines can initiate toxic manifestations and fatalities. The risk of adverse effects outweighs the benefit of antihistamine utilization in pregnancy. When used properly, antihistamines play an important role in the therapy of allergic disorders in children.

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Chapter 15

DRUGS IN GASTROINTESTINAL DISORDERS IN DEVELOPING INFANTS

Sam Kacew

TABLE OF CONTENTS

I. Introduction 266

II. Metoclopramide 266
  A. Pharmacokinetics 266
  B. Therapeutic Uses 267
  C. Mechanisms of Action 268
  D. Adverse Effects 269

III. Domperidone 270
  A. Pharmacokinetics 270
  B. Therapeutic Uses and Mechanisms of Action 270
  C. Adverse Effects 271

IV. Cimetidine 272
  A. Pharmacokinetics 272
  B. Mechanisms of Action 274
  C. Therapeutic Uses 275
  D. Adverse Effects 275

V. Ranitidine 276
  A. Pharmacokinetics 277
  B. Therapeutic Uses and Mechanisms of Action 277
  C. Comparison to Cimetidine 278
  D. Adverse Effects 279

VI. Aluminum Antacids 280
  A. Pharmacokinetics 280
  B. Role of Parathyroid Hormone and Vitamin D 281
  C. Factors Affecting Distribution in Body 282
  D. Adverse Effects 283
  E. Use of Deferoxamine as Antidote 284

References 286

I. INTRODUCTION

The etiology of certain diseases of the gastrointestinal (GI) tract of adults is now known to some extent. Unlike disease states associated with other organ systems, drug therapy has been effectively designed in gastroenterology. As a natural progression from adult to infant, effective drug therapy now exists for pediatric GI disorders. Although certain drugs discussed in this chapter have applications in diseases associated with other tissues, only the effect on intestinal function will be described. The agents elaborated upon in this chapter are the primary drugs utilized in pediatric GI disorders.

II. METOCLOPRAMIDE

One of the most effective drugs to emerge in the therapy of certain disorders associated with GI function is metoclopramide, methoxy-2-chloro-5-procainamide. Since its discovery as a central antiemetic agent,[1,2] metoclopramide is now categorized as a new generation dopamine antagonist.[3] In addition to the fact that metoclopramide is useful for GI problems associated with nausea and vomiting, this drug exerts direct actions on the hypothalamus and intestinal smooth muscle. The therapeutic applications of metoclopramide in neonatology and pediatrics are related to the actions of this dopamine antagonist at these tissue sites. It should be emphasized that exposure to metoclopramide can occur at the newborn stage via the lactational route[4] or in older infants due to direct administration.[5] Detailed, extensive reviews of the pharmacology of metoclopramide have already been published.[3,5] The emphasis of this section is to describe the actions of metoclopramide with relevance toward infants and children.

A. PHARMACOKINETICS

Despite the fact that metoclopramide has been prescribed for over 20 years, virtually little is known about the pharmacokinetic properties of this drug in newborns and children. When administered therapeutically to mothers after birth as a lactation-stimulating agent, metoclopramide was detected in breast milk.[6,7] In an extensive study, Kauppila et al.[7] found that metoclopramide levels were higher in maternal milk than plasma and that this drug was present in one out of five suckling newborns. Further, the peak maternal breast milk level was attained 2 to 3 h after metoclopramide administration, displayed a half-life of approximately 4 h, and did not accumulate to a significant extent. Similarly, Schulze-Delrieu[8,9] found that the plasma half-life of metoclopramide was about 4 h and that the bulk of the drug was excreted in urine unchanged or as the sulfate and glucuronide conjugate. It should be emphasized that the ability of newborns to undergo the process of glucuronic acid conjugation and renal excretion is less developed than in the adult.[7] At present, the significance and potential consequences of metoclopramide derived from breast milk on the newborn remain to be elucidated.

Renal excretion as a mechanism for the removal of drugs is immature in the newborn; thus, elimination of metoclopramide might be compromised.[7] Impairment in renal function was found to prolong the half-life of metoclopramide.[10,11] Bateman et al.[12] demonstrated that metoclopramide accumulation in adults with renal failure was not due to impairment of drug clearance by the kidney, but might be related to altered metabolism or change in enterohepatic circulation. Consequently, in patients with renal failure administered metoclopramide, the appearance of extrapyramidal side effects was noted.[13,14] Although it would appear that metoclopramide may accumulate in newborns where metabolism and renal excretion are not yet fully developed, no untoward effects were observed in infants whose mothers received therapeutic quantities of drugs and whose maternal kidney function was normal.[15] However, the potential adverse effects of metoclopramide accumulation in newborns and the known increased sensitivity to this agent[7] warrant caution with respect to the use of this compound in nursing children.[9] Recently, Sulyok et al.[16] administered low amounts of metoclopramide to preterm infants and noted enhanced sodium excretion accompanied by a decrease in urinary aldosterone secretion and reduction in urinary potassium excretion. The ramifications of these observations in developing children require further investigation in light of the fact that the dose inducing these metabolic disturbances in the renin-aldosterone system[16] is similar to the amount of drug accumulated in breast-fed infants.[15]

In addition to lactational exposure, accumulation of metoclopramide in the fetus and newborn can occur as a result of maternal drug ingestion during pregnancy. Metoclopramide has been prescribed to pregnant women suffering from hyperemesis gravidarum and as an antiemetic during anesthesia associated with Caesarean section.[5,17] Recently, Arvela et al.[18] administered metoclopramide to pregnant women prior to anesthesia for Caesarean section and detected the drug in umbilical venous and arterial plasma and in amniotic fluid. These results clearly demonstrated that metoclopramide readily crosses the placental barrier and that the concentration attained in fetal plasma was 60 to 70% of that in maternal plasma. It would thus appear that the fetus is exposed to a considerable extent to maternally administered metoclopramide,[18] yet the safety for the growing fetus has not been established.[9] It is of interest that while congenital malformations were not apparent in full-term or premature infants, metoclopramide produced drowsiness, diarrhea, glossitis, and oculogyric crisis in pregnant women.[5] Arvela et al.[18] emphasized that although no effect was apparent in the fetus, the ability of metoclopramide to transfer and accumulate in fetal tissue as well as attain high concentrations should warrant against free use of this drug in pregnancy.

As indicated previously, metoclopramide is a useful drug to be employed in certain situations in pediatrics other than a lactation promoter or antiemetic in pregnant women. Metoclopramide has been administered to children with pyloric stenosis, galactosemia, gastroenteritis, and hiatus hernia.[19] Sulyok et al.[16] administered metoclopramide to premature infants to treat delayed gastric emptying, regurgitation, and abdominal distension. In pediatrics, metoclopramide is also an effective agent in habit vomiting[19] and in vomiting associated with surgical anesthesia,[20] as well as in drug-induced vomiting.[21] Pharmacokinetic studies in infants revealed that metoclopramide is well absorbed and can initiate an adverse response within 30 min after a single intramuscular injection.[22] In general, metoclopramide exerts its effects within 36 h in children, but it may take as long as 120 h before a response is manifested in certain infants.[23,24] In view of the fact that children are more susceptible to the adverse effects of metoclopramide[9,23] and that the observed toxicity may be delayed in onset by 24 to 48 h, the absence of an immediate response should not be construed as an index to increase the dose or prolong the therapy.

B. THERAPEUTIC USES

The ability of metoclopramide to exert effects at different tissue sites is directly related to the diversity of its uses in pediatrics. In pediatrics, metoclopramide has been administered to treat minor GI ailments such as heartburn, dyspepsia, and abdominal pain, as well as gastric stasis and inflammatory processes associated with pyloric stenosis and hiatus hernia.[19,24] Various investigators[43,44] administered metoclopramide to infants to treat delayed gastric emptying, regurgitation, and abdominal distension. These symptoms are reflected as an inability of the infant GI system to carry out normal gastric motility and function. Essentially, metoclopramide is prescribed to correct the problems in infantile gastric motor failure. The gastrokinetic effects of metoclopramide include an elevation in GI resting muscle tension,[8,9] a rise in the size of contractions in the esophageal peristaltic ring gastric antrum and small intestine,[25,26] an increased pressure in lower sphincter of the esophagus and gastric fundus,[27] and an elevation in the coordination of mechanical activity of various gut segments characterized by relaxation of pylorus and duodenum during stomach contraction.[5,8,9] These

TABLE 1
Relationship Between Metoclopramide-Induced Effect and Transmitter Release

Response	Transmitter
Enhances GI motility	↑ Acetylcholine release
Increased GI motor function	↓ Dopamine action
Antiemesis	↓ Dopamine receptors in area postrema
Lactation	↑ Prolactin secretion
Increased GI motor activity	Direct (?)

Note: ? - unknown.

changes in motor activity result in functional or prokinetic effects of metoclopramide. Matuchansky et al.[28] showed that by decreasing the diameter of the gut lumen and by prevention of reflux, the increase in resting muscle tension promoted aboral movement of luminal contents. Metoclopramide hastened esophageal clearance, accelerated gastric emptying of contents, and shortened transit time through the small bowel.[9] Metoclopramide tended to produce coordination of antral and duodenal wave complexes, thus facilitating flow over long segments of gut and across organ boundaries. The observed enhancement in intestinal motility induced by metoclopramide was suggested to be responsible for the decrease in digoxin bioavailability.[236] It is evident that in cases where coadministration of digoxin and metoclopramide is necessary in infants, careful monitoring of digoxin is recommended to attain the desired effect.

In addition to an increase in gastric emptying rate, metoclopramide was found to elevate intestinal blood flow. Based on studies using rat duodenum and jejunum, Funaki et al.[228] demonstrated that metoclopramide increased GI absorption of cimetidine via an enhanced intestinal blood flow. In cases where drug absorption is incomplete due to inadequate intestinal blood flow, metoclopramide may be of potential benefit to the child.

C. MECHANISMS OF ACTION

The observed gastrokinetic and prokinetic effects of metoclopramide are believed to be related to an action on neurotransmitters in GI smooth muscle (Table 1). One of the mechanisms responsible for the excitatory motor phenomena induced in the gut by metoclopramide seems to be cholinergic activation. This is gained from the observation that postsynaptic activity results from the ability of metoclopramide to augment acetylcholine release from cholinergic nerve terminals in guinea pig stomach[29] and to sensitize human intestinal smooth muscle to the actions of acetylcholine.[30] In addition, evidence indicates that metoclopramide requires intrinsic stores of acetylcholine to initiate a response and that atropine can block the metoclopramide-induced increase in gut motility.[3,31,32] Although the therapeutic effectiveness of metoclopramide in GI dysfunction is primarily related to an action on cholinergic mechanisms in the gut,[8] there is evidence to suggest that inhibition of dopamine also plays a partial role. Dopamine is known to reduce the size of esophageal ring contractions, to relax the proximal stomach, and to reduce gastric secretions, effects which are blocked by metoclopramide.[33] Levodopa, a precursor of dopamine, inhibits gastric emptying and this effect is also antagonized by metoclopramide.[34] Similarly, apomorphine, a known dopamine agonist, in small doses produces gastric stasis and spasm of pylorus and duodenum, as well as constipation, and these responses are prevented by metoclopramide.[35] Finally, certain data suggest that metoclopramide exerts a direct action on the lower esophageal sphincter and on smooth muscle from the bladder, colon, and biliary tract.[3,9,36] Evidence thus suggests that modulation in either the cholinergic, dopaminergic, as well as direct action on intestinal smooth muscle, or a combination of systems may be responsible for the effectiveness of metoclopramide in pediatric GI disorders.

One of the major therapeutic applications of metoclopramide is as an antiemetic, be it in cases of habitual vomiting in the infant[19] or in drug-induced vomiting, especially in childhood cancer chemotherapy.[21] At present, the antiemetic effect of metoclopramide is believed to be central in origin based on the observation that this drug accumulates and is located in the area postrema, which contains the chemoreceptor trigger zone for vomiting.[3] Further, apomorphine or levodopa stimulate dopamine receptors in the chemoreceptor trigger zone to initiate emesis. It is of interest that metoclopramide is effective in antagonizing apomorphine- or levodopa-induced vomiting in humans.[5,37,38] All these findings taken together led Albibi and McCallum[3] to suggest that the antiemetic property of metoclopramide could be attributed to a direct inhibition of dopamine receptors located in the medullary chemoreceptor trigger zone.

The ability of metoclopramide to augment milk production is an important facet of its use in pediatrics. Various investigators have demonstrated that treatment with metoclopramide is effective in induction of lactation in women who develop lactational insufficiency.[4,39] The metoclopramide-stimulated increase in milk production is accompanied by an elevation in prolactin secretion.[15] It is known that dopamine is an inhibitor of prolactin secretion from the hypothalamus and that levodopa can block metoclopramide-induced prolactin secretion.[3,40] Evidence thus indicates that inhibition of dopaminergic receptors in the hypothalamus are related to the capacity of metoclopramide to enhance prolactin secretion and subsequently the process of lactation.

The immediate neonatal period has also been examined in infants with respect to the effect of metoclopramide on prolactin secretion. In full-term infants at a gestational age of 39 weeks, metoclopramide enhanced prolactin release.[45,46] In contrast, serum thyroxine and thyrotropin-releasing hormone levels remained unchanged after metoclopramide treatment. It was concluded that the dopaminergic control of endocrine function was already developed during the neonatal period and was subject to the influence of metoclopramide. The fact that metoclopramide exerts an action on a developed endocrine system is borne out by the finding that this drug stimulates the secretion of aldosterone in man.[47,48] This may present serious problems as metoclopramide may be administered as an antiemetic in women with hyperprolactinemia. O'Malley et al.[49] found that in females with hyperprolactinemia, the responsiveness to metoclopramide is exaggerated as evidenced by an enhanced sensitivity to circulating aldosterone. The potential consequences of chronic metoclopramide therapy during the neonatal period still need to be addressed. Clearly, the dopaminergic system is necessary for normal function; thus, suppression of this system may result in adverse effects.

D. ADVERSE EFFECTS

Metoclopramide is regarded as a comparatively safe drug in adults.[9,24] However, infants and children are particularly susceptible to the effects of metoclopramide and the recommended dose in adults has resulted in therapeutic poisoning.[23,24,42] In addition, there have been several reports of poisoning due to accidental ingestion of metoclopramide in infants and children.[5,23] Regardless of whether it is accidental or therapeutic poisoning, metoclopramide in infants and children produces agitation, irritability, and an extrapyramidal dystonia.[5,23] The extrapyramidal reactions consisted of dysarthria, torticollis, oculogyric crisis, facial grimace, opisthotonus, dyskinesias, and trismus.[21,23,24] The susceptibility to dystonic reactions to metoclopramide is also heightened in patients with renal impairment.[10,11] Thus, in certain children with renal failure, the potential for adverse extrapyramidal effects due to metoclopramide may be far more serious in comparison to normal children. The metoclopramide-induced dystonic effect was reversible in children as withdrawal of therapy resulted in a return to normal.[24,41] Treatment with either the anticholinergic agent, benztropine,[24] or the antihistaminic drug, diphenhydramine,[21] was also effective in the reversal of metoclopramide-induced extrapyramidal side effects in children. In essence, metoclopramide is a useful therapeutic agent in pediatric gastroenterology provided this drug is employed with caution, as children and infants appear to be more susceptible to the toxic actions of this compound.

III. DOMPERIDONE

Domperidone is a benzimidazole derivative with some similarities to the butyrophenone group of antipsychotic agents. This agent has proved to be extremely effective in counteracting a number of GI disorders in children and adults. The therapeutic usefulness of domperidone lies in the ability of this agent to block peripheral dopamine receptors.[50] The distinct advantage and attractiveness of domperidone over neuroleptics in the therapy of GI disorders are the inability of domperidone to cross the blood-brain barrier and that it does not produce resultant extrapyramidal side effects,[51] as seen with butyrophenone compounds. In light of the few reported studies in both adults and children, domperidone is considered to be a useful and safe agent for treatment of certain GI disorders.

A. PHARMACOKINETICS

Pharmacokinetic data indicate that domperidone is readily absorbed following oral, rectal, or intramuscular administration.[63] The onset of action is rapid, within 1 h, and the half-life is approximately 8 h.[63] Domperidone is metabolized by the liver and the metabolites are excreted via the bile.[63] In children, domperidone was also found to be easily absorbed as evidenced by a rapid onset of action.[65,66] At present, the metabolism of domperidone in children remains to be established.

A prominent basis for the therapeutic use of domperidone lies in the fact that this agent does not penetrate the blood-brain barrier. Metoclopramide resembles domperidone in that both drugs are dopamine antagonists and are utilized in pediatrics for similar GI disorders.[5] However, children are extremely susceptible to the central nervous system (CNS) disturbances associated with metoclopramide use.

B. THERAPEUTIC USES AND MECHANISMS OF ACTION

In a recent study, Grill et al.[52] administered domperidone to infants with gastroesophageal reflux associated with esophageal and gastric motor abnormalities. Domperidone proved effective in alleviation of the symptoms associated with gastroesophageal reflux. Since infants with severe gastroesophageal reflux also display prolonged gastric emptying and decreased amplitude of esophageal peristalsis,[53] it was suggested that the therapeutic effectiveness of domperidone may be attributed to increased efficiency of upper GI tract motility. This is supported by the finding that domperidone increased lower esophageal sphincter pressure, the major determinant of gastroesophageal reflux, as well as enhanced the amplitude of esophageal peristalsis and gastroduodenal motility in adults.[54] The mechanisms underlying the therapeutic usefulness of domperidone in gastroesophageal reflux are believed to be related to the role of dopamine at peripheral GI receptors. In studies using isolated stomachs from animals, several investigators have demonstrated that dopamine induces gastric relaxation[55,56] and decreases antroduodenal coordination,[57] the propagation of peristaltic waves from antrum over pylorus to the duodenum. In the presence of domperidone, the GI effects of dopamine were blocked, clearly indicating that the gastrokinetic actions of domperidone are due to dopamine antagonism at peripheral sites. Domperidone is considered to be a potentially important drug of the future as this agent alleviates the motility abnormality inherent in the pathophysiology of gastroesophageal reflux and does not simply provide symptomatic relief.[52]

Some forms of dyspepsia are associated with abnormal GI motility as evidenced by a delay in gastric emptying. The pyloric sphincter is believed to play an important role in the regulation of gastric emptying.[58] It is thus not surprising that Platteborse et al.[59] found that domperidone was effective in treatment of dyspepsia in adults. In their study,[59] domperidone increased gastric emptying by enlargement of the pylorus at the moment of maximal opening and attenuation of antral contractions. In agreement with these findings, several other investigators have shown that domperidone is effective in alleviation of symptoms associated with chronic dyspepsia.[60,61] While the precise underlying cause of dyspepsia was not established, van Ganse et al.[61] found that the symptoms were related to a delay in gastric emptying. Data thus suggest that domperidone is useful in chronic dyspepsia due to an action on GI motility.

In humans an acceleration in the rate of gastric emptying was also reported by Broekaert.[62] In a subsequent study, Bateman et al.[69] found that domperidone decreased the volume of the stomach, but not the rate of gastric emptying. Despite the lack of change in rate, the reduction in volume was associated with increased gastric motility. The finding that domperidone blocked the delay in gastric emptying induced by apomorphine, a compound known to act via dopamine, suggests that the mechanism responsible for the observed effect is also due to dopamine antagonism. In addition to dyspepsia, idiopathic gastric stasis affects the ability of the individual to empty stomach contents. In patients with symptomatic gastroparesis, domperidone was reported to accelerate gastric emptying and alleviate the adverse symptoms.[51] Although data are not available for children, evidence suggests that domperidone stimulates gastric emptying and would prove useful in pediatric GI disorders associated with upper GI motor dysfunction. It is of interest that domperidone exerts a specific effect on intestinal motility as gastric acid and pepsin secretion is not altered.[54,62] Weihrauch et al.[54] suggested that in the treatment of peptic ulcer the lack of gastric acid release would certainly be of benefit to the patient.

An important therapeutic use of domperidone to emerge in recent years is the treatment of nausea and vomiting, irregardless of the underlying cause. In an extensive review, Reyntjens[63] reported that domperidone was effective as an antiemetic prior to surgery or radiotherapy and in postprandial nausea and vomiting. Domperidone prevented nausea and vomiting associated with conditions such as dysmenorrhea, migraine, and head injuries and blocked drug-induced emesis. As in the case of the adult, Dhondt et al.[64] reported that domperidone was effective in blockade of nausea and vomiting in hospitalized children suffering from gastroenteritis and respiratory infections, as well as vomiting of acetonemic and nervous origin. In infants and children with severe vomiting attributed to regurgitation, several investigators demonstrated that domperidone was effective in controlling the observed symptoms.[65,66] The role of dopamine in the genesis of vomiting is poorly understood. However, Dhondt et al.[64] postulated that the mechanism of action of domperidone as an antiemetic agent may be related to a blockade of dopamine receptors located at peripheral GI sites.

C. ADVERSE EFFECTS

Treatment of children with domperidone was reported to produce minimal or no adverse effects.[52,65] It should be mentioned that in a 4-month-old infant administered domperidone, a manifestation of extrapyramidal motor disturbances occurred.[67] In addition, treatment of an infant boy with domperidone was found to produce gynecomastia and galactorrhea which was attributed to enhanced prolactin secretion.[68] Grill et al.[52] reported that domperidone increased serum prolactin levels, but no evidence of breast enlargement, galactorrhea, or extrapyramidal side effects was noted. Clearly, the bulk of evidence suggests that domperidone is a safe compound and the potential usefulness of this drug in pediatric GI disorders certainly merits further investigation.

IV. CIMETIDINE

Since the discovery of a group of compounds that can block histamine-induced gastric acid secretion,[70] cimetidine has emerged as a therapeutically important agent in pediatric gastroenterology. The receptors blocked by cimetidine were classified as H_2 receptors and hence this drug is categorized as a histamine H_2 receptor antagonist.[71] Chemically, cimetidine contains an imidazole ring similar to histamine; however, the side chain is modified and lengthened. The rationale for the therapeutic use of cimetidine in children is based on the ability of this drug to inhibit gastric secretory processes. Although cimetidine has been employed in pediatrics in critically ill and burn patients, relatively few studies are documented on the pharmacokinetics and adverse effects of this H_2 receptor blocker in infants. The focus of this discussion will center on the reported effects of cimetidine in children. While it would be convenient to extrapolate data from adult studies and apply it to infants and children, this is not feasible as the pediatric patient is not a miniature adult in terms of pharmacodynamics and responsiveness to drugs.[72] A detailed review of the pharmacology of cimetidine in adults is provided by Freston.[73,74]

A. PHARMACOKINETICS

Cimetidine has been advocated for the treatment of a variety of GI disorders in children. In pediatric patients, cimetidine can be administered using either the intravenous, intramuscular, or oral route.[73] The route of administration chosen is dictated by the condition of the patient as in the case of critically ill children where the intravenous route is preferred. Similarly, age plays a role in the administration route of cimetidine as in neonates the drug is given intravenously. However, cimetidine has been administered orally as early as 8 weeks of age in some infants.[75]

An oral preparation of cimetidine was administered by Chhattriwalla et al.[75] to infants with either reflux esophagitis or gastric and duodenal ulcers. At present, the pharmacokinetics and metabolism of cimetidine following oral administration to children remain to be established. However, in adults cimetidine is completely absorbed after oral administration and possesses a half-life of 2 h.[73,77] Cimetidine is excreted primarily unchanged in the urine, although approximately 15% undergoes hepatic metabolism.[73] Since neonates may have reduced renal function due to a pathological disorder or simply due to developmental delay,[76] cimetidine may accumulate with a resultant manifestation of adverse reactions. Indeed, Ma et al.[78] demonstrated an accumulation of cimetidine in adults given this drug in the presence of renal failure. Although the adults with renal failure appeared to tolerate a single dose of cimetidine as evidenced by a lack of adverse effects,[78] this does not lessen the potential for drug toxicity in newborns or children.

In pancreatic insufficiency due to cystic fibrosis, cimetidine is administered orally as an adjunct to pancreatic enzymes to prevent gastric acidity from destruction of these latter enzymes.[79] The oral administration of cimetidine to children with cystic fibrosis resulted in the attainment of blood levels similar to those seen in normal volunteers.[80] In contrast, Bradbear et al.[81] found that cimetidine reached far higher concentrations in the plasma of children with cystic fibrosis. At present, the precise pharmacokinetics of cimetidine in pediatric patients with cystic fibrosis require further investigation. If, as the study of Bradbear et al.[81] suggests, there is a prolonged half-life for cimetidine in the condition of cystic fibrosis, this may result in toxic manifestations. However, the use of cimetidine in pediatric cystic fibrosis patients was reported not to be associated with any significant adverse effects.[81,82] The lack of any apparent untoward effects may be related to the short term of therapy.[81]

Considerably less information is available on the kinetics and distribution of cimetidine following oral administration in infants. In children administered cimetidine preoperatively prior to anesthesia to reduce gastric acidity to protect lungs from accidental aspiration, Goudsouzian et al.[99] found that 1 h was required for the drug to produce an effect. However, the dose necessary to decrease gastric fluid volume and pH was significantly less than that found in the adult. Goudsouzian et al.[99] suggested that cimetidine is more effectively absorbed in children, resulting in a subsequent higher bioavailability. Although the distribution of cimetidine following oral administration needs to be addressed, data from adult studies indicate that this drug is widely distributed throughout the mammalian organism, predominantly in skeletal muscle.[100] In addition, there is extensive uptake into kidney, lung, and muscle. Of particular interest is the finding that cimetidine is present in cerebrospinal fluid, which may be associated with the observed cerebral toxicity reported in children.[101]

As indicated previously, the intravenous route of administration has been utilized for the management of GI tract bleeding associated with increased gastric acidity in premature and term neonates.[83,84] Aranda et al.[83] reported that the plasma half-life of cimetidine given intravenously to raise the gastric pH in the premature newborn with impaired renal function was 2.6 h. Similarly in the term infant, Ziemniak et al.[85] found that the half-life for cimetidine administered intravenously was 2.4 h. It is of interest that the observed half-life of cimetidine in these studies[83,85] was similar to that obtained in the critically ill adult (2.27 h)[77,86] and higher than that in the adult with peptic ulcer (1.8 to 2.0 h).[86,87] In contrast, Lloyd et al.[84] demonstrated that in a 10-day-old neonate administered cimetidine for the management of GI hemorrhage, the half-life was prolonged to 3.6 h. As the infant developed to an age of 5 to 13 years, the half-life of cimetidine administered for treatment of gastric hypersecretion was only 1.4 h,[88] which reflects a more rapid elimination than in the adult.[86] These data clearly demonstrate that cimetidine clearance is increased in children and may be related to enhanced renal elimination mechanisms. In neonates where renal development is immature and far more variable,[76] the elimination kinetics were either prolonged or similar to that seen in a critically ill adult. Since the effectiveness and potential adverse reactions of cimetidine in the management of GI bleeding are dependent on drug concentration, it is crucial to consider the stage of infant development in therapeutic application.

The intravenous route of cimetidine administration is also employed on a prophylactic basis in a pediatric population referred to as critically ill children. As a consequence of severe burns, surgery, trauma, or corticosteroid therapy, children can develop gastroduodenal ulceration.[89-91] It should be emphasized that children are far more susceptible to stress-induced duodenal ulceration in comparison to adults.[92] This so-called stress-induced ulceration in infants leads to a secondary yet serious consequence as manifested by upper GI tract bleeding. Hence, cimetidine is administered on a prophylactic basis in a pediatric intensive care unit in cases of trauma and burns.[89,93] In recent years, the pharmacokinetics of cimetidine in critically ill children has been the focus of several studies. Chin et al.[94] found that in 82 critically ill children ranging in age from 2 to 12 years, the elimination half-life of cimetidine was 1.4 h, which is considerably less than that found in the newborn or in the adult. Similarly, in a group of 30 critically ill children with an approximate mean age of 9 years, Lloyd et al.[95] reported a cimetidine elimination half-life of 1.39 h. These studies clearly demonstrate that cimetidine clearance is enhanced in critically ill children and that the drug dosage must be adjusted in these infants in order to adequately control gastric acid secretion.

At present, the bioavailability of cimetidine following intravenous administration to infants and children has not been reported. Regardless of the amount of bioavailable drug, Aranda et al.[83] demonstrated a fast and sustained increase in gastric pH in the premature newborn in response to cimetidine. In contrast, Stothert et al.[102] were not able to raise the gastric pH in a group of adults with stress ulcer. Aranda et al.[83] thus suggested that the newborn may be more susceptible to the action of cimetidine; hence, even though 60% may be bioavailable, as in the adult,[103] the neonate is more responsive. An enhanced susceptibility to cimetidine action was also found in older children.[99] Following intravenous administration, approximately 60% of cimetidine is excreted unchanged in urine of children,[90] which is similar to that reported for adults.[86,104] Recently, Lloyd et al.[84,95] demonstrated the presence of cimetidine sulfoxide and hydroxymethyl cimetidine in plasma of a full-term infant and critically ill children. Similarly, Ziemniak et al.[85] also found that cimetidine underwent metabolism to the sulfoxide metabolite in infants. The half-life of cimetidine metabolites was of longer duration than the parent compound in critically ill children.[95] In contrast to the adult, where guanylurea cimetidine was detected as a metabolite,[104] this metabolite was not found in any plasma sample in children.[84,95] The importance of establishing the pharmacokinetics of cimetidine in pediatrics lies in the fact that therapeutic failure may be averted by simple adjustment of dose with the knowledge that, for example, elimination is greater in a child.[90]

Finally, the other routes to consider in neonatology are exposure of the fetus via the placenta and newborn via breast milk, Howe et al.[96] determined cimetidine levels in venous cord and umbilical cord blood of fetuses from mothers administered a single dose of drug during obstetric anesthesia to reduce gastric acidity in patients undergoing Caesarean section. The presence of cimetidine in fetal plasma was indicative that placental transfer did occur. Further, the finding that cimetidine levels in neonatal plasma exceeded those in the mothers suggested that there was substantial uptake by the fetus, presumably because elimination processes were not as effective as in the adult.[88] The use of a single dose of cimetidine during pregnancy did not appear to adversely affect the fetus[98] and the placenta seems to provide a significant barrier to the movement of cimetidine.[245] However, in order to raise the intragastric pH and maintain a satisfactory reduction in gastric acidity during obstetrical anesthesia, cimetidine must be administered repetitively. The consequences of placental cimetidine exposure on the fetus and developing newborn associated with repetitive administration are still not known. In a nursing mother with a duodenal ulcer, the administration of cimetidine resulted in drug accumulation in breast milk in a higher concentration than maternal plasma.[97] It is of interest that greater accumulation occurred in breast milk with repeated cimetidine administration, whereas in plasma the concentration did not rise with successive treatment. Somogyi and Gugler[97] suggested that excessive accumulation in breast milk with repeated cimetidine administration was entirely unpredictable from the known pharmacokinetic properties of this agent. Clearly, the clinical relevance of this finding needs to be addressed as the lactational route would appear to expose a newborn to high amounts of cimetidine.

B. MECHANISMS OF ACTION

The mechanism by which cimetidine blocks gastric acid secretion in children or adults remains unresolved. With the use of isolated parietal cells, Soll and Grossman[105] identified specific histamine receptors and suggested that cimetidine specifically inhibited histamine-induced gastric acid secretion. However, cimetidine was ineffective in antagonism of gastrin- or acetylcholine-stimulated gastric acid secretion. In association with a reduction of gastric acid secretion, cimetidine was found to decrease the output of pepsin.[106] It has also been postulated that the ability of intravenous cimetidine administration to interact with a subdivision of H_2-histamine receptors may be responsible for the observed increase in prolactin release and secretion.[107,108] It is of interest that cimetidine ingested orally does not affect prolactin secretion.[109] Although dopamine antagonism at the hypothalamic-hypophyseal level may be involved in cimetidine-stimulated prolactin release,[110] it would appear that inhibition of H_2-histamine receptors is an integral component in this response.[108] At present the relationship between the ability of intravenous cimetidine to stimulate prolactin secretion and the excessive accumulation of this drug in breast milk is not known.

A pharmacological phenomenon which may be of clinical relevance in pediatrics is the

TABLE 2
Therapeutic Uses of Cimetidine in Pediatrics

Route of administration	Use
Oral	Reflux esophagitis
Oral	Gastric and duodenal ulcers
Oral	Pancreatic insufficiency associated with cystic fibrosis
Oral	Preoperatively to reduce gastric acidity
Intravenous	Management of GI bleeding
Intravenous	Prophylactically to prevent ulceration due to burns, trauma, surgery
Oral (maternal)[a]	Obstetric anesthesia to reduce gastric acidity

[a] Administered to pregnant women; however, fetus exposed via breast milk.

effect of the cimetidine on hepatic drug-metabolizing enzymes. In the therapy of various childhood GI disorders, cimetidine is frequently administered in conjunction with other drugs.[89] In the adult patient, cimetidine was found to interfere with the metabolism of warfarin, diazepam, and theophylline, resulting in a potentially higher risk of side effects.[111-113] In the case of warfarin and theophylline, where cimetidine was found to enhance the effect of these drugs, it was recommended that concurrent use be avoided.[111,113] Henry et al.[114] demonstrated that cimetidine was effective in inhibiting human liver microsomal drug-metabolizing enzymes and suggested that enzyme inhibition was not associated with blockade of H_2-histamine receptors. It should be emphasized that several investigators believe that cimetidine will interact with numerous other drugs and the consequences may be clinically relevant.[115,116,163,243] The hepatic drug-metabolizing enzyme system is not fully developed in infants and children.[117] As children appear more responsive to cimetidine and multiple drug therapy is common, interference with hepatic drug metabolism may result in serious adverse reactions. Interference with hepatic drug metabolism is not the only mode by which cimetidine affects the concentration of other drugs. Recently, Cox et al.[229] demonstrated that cimetidine increased the plasma concentration of the benzodiazepine, triazolam. The mechanism responsible was not attributed to a reduction in hepatic metabolism, but was associated with a delay in oral clearance. The significance of this type of interaction for the pediatric patient needs to be addressed.

C. THERAPEUTIC USES

The major indication for cimetidine use in pediatrics is for the prophylaxis of stress- and steroid-induced ulcers and associated GI bleeding.[89] Similarly, this is the primary reason for the prescription of cimetidine in the adult population.[118] In addition, cimetidine has proved to be therapeutically effective in a variety of GI disorders (Table 2). In general, cimetidine therapy in pediatrics is of short duration, lasting approximatley 8 d; however, this drug is usually administered concurrently with other agents.[89] Clearly, adverse reactions occur as a result of cimetidine use, but one cannot in numerous cases conclusively state that an observed untoward response is specifically due to the H_2 antagonist based on the multiple drug regimen.

D. ADVERSE EFFECTS

An excessive amount of cimetidine was reported by Thompson and Lilly[101] to produce infant cerebral toxicity as manifested by impaired consciousness and decreased spontaneous movements. Aranda et al.[83] noted a mild neurologic and developmental delay at 16 months in a premature newborn given cimetidine at 25 weeks of gestation. Other signs of CNS toxicity attributed to cimetidine use in children include confusion, hallucinations, hysteria, drowsiness, and seizures.[89] It would appear that the very young patients as well as the elderly display CNS dysfunction more frequently in response to cimetidine.[74,119] Although the bulk of studies suggests that cimetidine is a relatively safe, effective drug, one should be aware that the susceptibility to adverse cerebral effects is enhanced in pediatric patients.

In an extensive study, Milochik et al.[89] correlated cimetidine use in pediatrics with the appearance of adverse effects. In addition to signs of CNS toxicity, cimetidine treatment was associated with cardiac dysrhythmias, in particular bradycardia and irregular sinus rhythm. Cimetidine use has also been attributed to result in bradycardia in adult patients.[120] However, cardiovascular toxicity appears to be rare in the adult and occurs only upon rapid intravenous bolus infusion of the drug.[74] The pediatric patient population utilized by Milochik et al.[89] in which cardiac abnormalities were observed most likely also received a rapid intravenous infusion. Hence, in situations where underlying cardiovascular disease is suspected, the rapid intravenous infusion route should be avoided in children.

The most frequently reported adverse effects in adult patients consist of diarrhea, nausea, and vomiting,[121] symptoms observed in the child. Similarly, skin eruptions characterized by rash, hives, and pruritus are associated with cimetidine use regardless of age. Although hematologic toxicity, including thrombocytopenia and neutropenia, has been reported following cimetidine administration in the infant and adult,[89,122] there is a lack of evidence that cimetidine alone was responsible for this adverse effect.[74] In the adult male, cimetidine was found to produce gynecomastia.[123] However, this abnormal endocrine response has as yet not been reported in the pediatric human patient or in the male rat offspring of pregnant dams given cimetidine in drinking water from day 12 to lactation.[250] It should be emphasized that the severity of the adverse reaction produced by cimetidine was related to the duration as well as to the number of concomitant drugs. An increase in either the duration or number was associated with enhanced severity in adverse reactions. Although prolonged cimetidine use is associated with disturbances in CNS and endocrine function, treatment with this H_2 blocker for 7 years produced no evidence of gastric cancer in dogs.[162]

The continued increasing use of cimetidine in pediatrics demands that the pharmacokinetic and pharmacodynamic properties be firmly established. In this manner, the incidence and severity of adverse effects could be reduced while the range of therapeutic effectiveness may be increased. Clearly, cimetidine has proven to be an integral tool in pediatric gastroenterology in the treatment of a variety of disorders.

V. RANITIDINE

In the search for a more potent and selective antagonism of H_2 histamine receptors, the drug ranitidine was discovered. Chemically, ranitidine is a substituted alkyl furan derivative of histamine and does not contain an imidazole ring.[124] Since the *in vitro* findings that ranitidine was capable of blocking the histamine H_2-receptor-induced increase in contraction frequency of guinea pig right atrial muscles and rat uterus,[125,126] this drug has undergone extensive study in humans as a potential agent to be used in peptic ulcer disease.[127] As in the case of cimetidine, the pharmacology, therapeutic usefulness, and adverse effects have been extensively reviewed for the adult patient population.[127-130] Despite this vast amount of knowledge in the adult, virtually little information is available describing the use of ranitidine in pediatrics. It should again be emphasized that an infant or child does not respond to drugs in an identical manner as the adult.[8] Although the focus of this article is aimed at the pediatric patient, certain portions of this text are dependent on information from adults, as studies with children have yet to be done.

A. PHARMACOKINETICS

In view of the relative safety and therapeutic usefulness of ranitidine, a detailed pharmacokinetic study was undertaken by Blumer et al.[137] in children ranging in age from 3 to 16 years with documented gastric or duodenal ulcer. In children studied, the half-life of ranitidine following oral or bolus intravenous therapy was approximately 2 h. In the adult, the half-life of ranitidine following bolus intravenous administraiton is also approximately 2 h, but is increased to 3 h using the oral route.[152,153] Although there appears to be a difference with respect to elimination half-life in relation to age, the bioavailability still averaged 50% in children or adults given ranitidine orally.[137,153] It is worthy to note that in conditions of chronic liver disease in adults, the serum concentration of ranitidine is significantly enhanced due to an increase primarily in bioavailability.[154] In contrast a reduction in clearance is believed to be mainly responsible for the elevation in ranitidine half-life in adult patients with renal disease.[155] The pharmacokinetics of ranitidine in children with liver or kidney disorders is at present not known.

Although further investigation is necessary, the pharmacokinetic findings of Blumer et al.[137] suggest that children are more responsive pharmacologically to ranitidine. In pediatric patients administered ranitidine, the attainment of serum levels of 40 to 60 ng/ml was associated with 90% inhibition of gastric secretion. However, in adults serum ranitidine concentrations of 100 ng/ml could only effectively block gastric acid secretion by 50%.[136,153,156] Data thus demonstrate that regardless of dose, there is more effective inhibition of gastric acid secretion in children. Further, Blumer et al.[137] demonstrated that the pharmacological action desired in pediatric patients is reached at far lower concentrations, suggesting that ranitidine may be safer in this population. It is of interest that no adverse clinical or biochemical effects were noted after 6 weeks while the initial ulcer was completely healed.

In a recent study, Prichard et al.[160] demonstrated that the ability of ranitidine to inhibit gastric acid secretion decreased with continued therapy. It was suggested that the sensitivity of acid-secreting mechanisms to ranitidine was reduced in adults administered the drug over a 9-month period. Similarly, in infants with malabsorption syndrome, Hyman et al.[235] demonstrated the phenomenon of tolerance to inhibition of acid secretion by long-term ranitidine administration. Data suggest that the desired effect may be attained in the pediatric population only after short-term therapy. Further, tolerance may play an important role in the more rapid recurrence of peptic ulcers in infants administered ranitidine.[235]

The distribution of ranitidine which has relevance to pediatrics as a route of entry is that fraction present in breast milk. In puerperal patients administered a single oral dose of ranitidine, Riley et al.[157] demonstrated that this H_2-receptor antagonist penetrated into breast milk. It is of interest that the ratio of ranitidine in breast milk to plasma was 2:1 after 2 h and reached 6:1 after 8 h. Unfortunately, the infants of these treated mothers were not examined. As the kidney and liver function of lactating infants is not fully developed,[72] further study is warranted on the effects of lactational ranitidine exposure on growing children.

B. THERAPEUTIC USES AND MECHANISMS OF ACTION

The rationale for the therapeutic use of ranitidine in pediatrics is based on studies in animals and adult humans. Treatment with ranitidine was found to inhibit gastric secretion induced by histamine, pentagastrin, bethanechol, or a test meal.[126,131] Similarly in normal adult healthy volunteers, ranitidine was reported to prevent histamine-, pentagastrin-, or cholinergic-stimulated gastric acid secretion,[132,133] as well as basal gastric acid secretion.[134] As expected in adult patients with duodenal ulcer, ranitidine was effective in the blockade of basal and pentagastrin-stimulated gastric acid secretion.[135,136] In addition, ranitidine significantly reduced the recurrence rate of gastric ulcers.[244] In a recent study in children inflicted with gastric or duodenal ulcer, Blumer et al.[137] demonstrated that ranitidine was effective in suppression of gastric acid secretion. Data thus suggest that ranitidine exerts a similar pharmacological action in children and adults with respect to inhibition of gastric acid secretion. It is of interest that ranitidine is more potent than cimetidine in suppression of gastric acid secretion in normal and adult duodenal ulcer patients.[138,139] Although the phenomenon of potency remains to be established in pediatrics, it would appear that in children administered equipotent amounts of cimetidine and ranitidine, the latter drug would produce a greater degree of suppression of gastric acid secretion.[130]

The precise mechanism underlying ranitidine-induced inhibition of gastric acid secretion is not known. It is believed that secretion of acid by the stomach is associated with binding of gastrin, acetylcholine, and histamine to their respective receptors located on the parietal cell surface.[73,130] Since ranitidine is known to prevent pentagastrin-, acetylcholine-, or histamine-stimulated gastric acid secretion,[127,130] the H_2 receptor antagonist has been proposed to block the effect of the secretogogue on its parietal cell receptor. The similarity in responsiveness between children and adults suggests an identical mechanism of action at the parietal cell regardless of age.

In children with reflux esophagitis, Socha et al.[140] demonstrated that ranitidine decreased the frequency and severity of heartburn and retrosternal pain. Recently, Goudsouzian and Young[246] administered ranitidine preoperatively to healthy children presented for sugrical procedures. Ranitidine was effective in the reduction of gastric acidity, but unlike the adult, there was no significant effect on gastric aspirate volume. The finding by Bertaccini et al.[141] that ranitidine produced an increase in lower esophageal sphincter pressure suggested that in addition to suppression of gastric acid secretion, this factor may play a role in the therapeutic effectiveness of this drug in this condition. In a subsequent study, Wallin et al.[142] found that ranitidine failed to affect esophageal sphincter pressure. While the underlying mechanism remains to be elucidated, ranitidine was reported to resolve the symptoms of reflux esophagitis in all pediatric patients examined.[140]

Acute pancreatitis refers to a condition characterized by the destruction of the pancreas and has been attributed to the escape of lytic pancreatic enzymes to the pancreatic parenchyma. Ranitidine administration to children aged between 4 and 18 years with acute pancreatitis was found to resolve the symptoms in these patients.[140] However, ranitidine treatment did not affect pancreatic secretion.[143] In addition, the pancreozymin- or secretin-stimulated increase in pancreatic protein secretion was not altered in the presence of ranitidine.[144] Clearly, the therapeutic effectiveness of ranitidine in acute pancreatitis in pediatric patients appears not related to a release of pancreatic lytic enzymes into the pancreatic parenchyma. Since gastric acid secretion was blocked in children with acute pancreatitis, the usefulness of ranitidine in this condition may be associated with elimination of manifestations attributed to acidity and independent of lytic enzyme release in pancreas.

C. COMPARISON TO CIMETIDINE

A comparison between the pharmacological actions of ranitidine with cimetidine clearly delineates the basis for the rapid and preferred growth of ranitidine in pediatrics (Table 3). In certain cases, children require a combination of drugs for the treatment of various disorders. Henry et al.[114] demonstrated that ranitidine failed to markedly alter hepatic drug metabolism and hence the clearance of specific agents. Further, ranitidine was reported not to prolong the half-life of propranolol and lidocaine.[145,146] While cimetidine increased the bioavailability of the antihypertensive agent, nifedipine, ranitidine did not produce any significant change.[164] In contrast to cimetidine which produces inhibition of hepatic drug-metabolizing enzymes and consequent adverse reactions, ranitidine appears to be safer in patients of all ages taking drugs that require liver degradation.[130] An extensive review of ranitidine drug interactions has recently been published by Mitchard et al.[247]

Ranitidine, unlike cimetidine, was shown to lack the ability to displace dihydrotestos-

TABLE 3
Pharmacological Differences Between Ranitidine and Cimetidine

Effect	Ranitidine	Cimetidine
Inhibition of hepatic microsomal enzymes	—	↑
Prolongation propranolol half-life	—	↑
Prolongation lidocaine half-life	—	↑
Gynecomastia	—	↑
Binding to androgen receptors	—	↑
Stimulation of prolactin secretion	—	↑
Bioavailability affected by aluminum antacid	↑	—

Note: —: denotes lack of apparent effect; ↑ : denotes presence of effect.

terone from androgen binding sites and failed to markedly alter basal testosterone levels in serum.[147,148] The apparent lack of affinity of ranitidine for androgen receptors is believed to be responsible for the observation that this drug does not produce gynecomastia,[130,147] an adverse effect seen with cimetidine.[74] Similarly, various investigators demonstrated that ranitidine does not stimulate prolactin secretion and did not significantly increase serum prolactin levels,[108,149] a side effect encountered with cimetidine.[74] It is of interest that ranitidine did not only fail to induce adverse reactions, but that substitution of this drug in patients initially administered cimetidine resulted in a disappearance of gynecomastia and leukopenia.[150,151] Regardless of age, it would appear that ranitidine is a more potent and safer drug than cimetidine in the treatment of duodenal ulcer.[161] In addition, data suggest that ranitidine may be substituted for cimetidine in children without incurring adverse reactions due to other drugs such as propranolol, diazepam, lidocaine, or doxepin.[130,237] In therapy, situations can arise where the bioavailability of ranitidine may be diminished. In a recent study, Albin et al.[230] found that in adults concurrently administered ranitidine and aluminum phosphate, the bioavailability of the H_2 blocker was diminished. In contrast, aluminum antacid did not reduce the bioavailability of cimetidine.[231] Based on the interaction between aluminum antacid and ranitidine,[230] these two agents should not be coadministered to children.

D. ADVERSE EFFECTS

The increased usage of ranitidine in the treatment of GI disorders in children has not been associated with a rise in the reported incidence of side effects. Of the few documented studies published, the short-term use (4 to 6 weeks) of ranitidine was accompanied by no adverse clinical or biochemical effects.[137,140] Similarly, the exposure of nursing infants to ranitidine via the breast milk appeared not to adversely affect the child.[157] It is thus not surprising that the incidence of side effects in adults which include headache, nausea, and skin rash is less than 3% in the patient population.[158,159] Clearly, ranitidine appears to be a safe drug which produces minor side effects. It should be emphasized that the potential toxicity of ranitidine increases in patients with renal impairment or chronic liver disease.[154,155] The use of ranitidine in children with kidney or liver disease has not been documented. However, in view of the increased susceptibility of children to the pharmacological actions of ranitidine, the potential for adverse effects may be accentuated in the presence of renal or hepatic disease. The lack of in-depth knowledge concerning ranitidine emphasizes the need for further study as the usefulness of this drug is gaining prominence in GI therapeutics.

TABLE 4
Potential Aluminum Sources for Children

Source	Ref.
Drug	166, 168, 183
Municipal drinking water	165, 167
Soil and water in Guam	222, 223
Parenteral nutrient	217, 218
Breast milk	213

VI. ALUMINUM ANTACIDS

One of the most abundant elements present in the crust of the earth is aluminum. Although aluminum may be considered as an environmental agent, this metal plays a role in therapeutics, particularly in pediatric nephrology. The utilization of aluminum-containing compounds in infants with renal disease, while serving to bind phosphate in dialysis therapy, has been implicated in the etiology of a number of clinical manifestations.[165,166] Despite the fact that aluminum is an environmental contaminant, inclusion of this element is based on its therapeutic application in pediatric nephrology.

In adults, aluminum is an important consituent of the ''over-the-counter'' class of drugs used in the treatment of gastric ulcers. Based on their ability to neutralize acid in the stomach, aluminum-containing compounds are categorized as gastric antacids. The capacity to bind and neutralize phosphate is the rationale for addition of aluminum-containing antacids to dialysate in neonatology[183] and this mode serves as the prime source of this element in children.

The environment also contributes to the body burden of aluminum in infants. In municipal water supplies, aluminum sulfate or alum is added as a flocculating agent in the process of water purification.[165] Clearly, in the preparation of dialysate, the use of municipal drinking water would contain aluminum. Hence, tap water would be considered as an environmental source of aluminum[167] with far-reaching implications in pediatric toxicity as exposure is not intentional. Indeed, McDermott et al.[185] suggested that aluminum-induced encephalopathy was related to the presence of this metal in the dialysate originating from the municipal water supply, as this syndrome did not occur in patients dialyzed with noncontaminated water. This observation is supported by the findings that individuals living in an area in Guam, where the aluminum content in soil and water was found to be high, developed a neuropathological syndrome resembling Parkinson's disease.[222,223] It is of interest that the concentration of aluminum was elevated in the hippocampus of these Parkinsonian-like patients.

Recently, it has been shown that in infants requiring parenteral nutrition following surgical procedure, the body burden of aluminum was elevated.[217] In a subsequent study, Koo et al.[218] increased the aluminum load in infants receiving parenteral nutrition and noted elevated aluminum levels in serum and bone accompanied by decreased urine metal excretion. These data demonstrated that parenteral nutrition solutions are a further source of aluminum contamination in children. In conditions of renal dysfunction, the parenteral nutritional source of aluminum can result in toxicity as assessed by aluminum accumulation in bone. In essence, the sources of aluminum for the child can be either nutritional, pharmacologic, or environmental, or a combination of both (Table 4), leading to increases in body burden and potential drug toxicity.[238]

A. PHARMACOKINETICS

The therapeutic usefulness and toxicity of aluminum-containing drugs is highly dependent on the functional status of the infant. The fraction of aluminum absorbed from aluminum-containing antacids is approximately 1 to 2% of the initial orally administered dose.[168] The bulk of ingested aluminum is eliminated in the feces, while a minor portion is excreted in urine. In children with normal renal function, the serum concentration of aluminum can reach values of approximately 10 μg/l, following oral administration of aluminum hydroxide.[169] However, in children undergoing continuous ambulatory peritoneal dialysis (CAPD) and simultaneously given aluminum hydroxide orally, Salusky et al.[169] noted that the serum aluminum level rose to 55 μg/l. Of greater concern was the observation that the serum concentration of aluminum was substantially higher (approximately 200 μg/l in the youngest patient. Exceedingly high levels of serum aluminum (>150 μg/l) have been reported by a number of investigators in children.[170,171]

Regardless of the status of kidney function, data suggest that the fractional intestinal absorption of aluminum is higher in young children[169] and, hence, of greater risk to the normal infant as compared to the adult. In conditions of severe renal impairment where there is a decrease in glomerular filtration rate, GI absorption of aluminum is even further accentuated.[166,172] In a recent study, Milliner et al.[225] compared aluminum accumulation in children undergoing hemodialysis vs. CAPD. The level of aluminum was equally elevated above normal in pediatric hemodialysis and CAPD patients. Based on the potential for serious aluminum toxicity, it was suggested that alternative methods for control of serum phosphorous are necessary in children with end-stage renal disease.

The intestinal absorption of aluminum is dependent on both kidney function and infant age. Further, the finding by Weberg and Berstad,[214] that citric acid markedly increased aluminum antacid absorption from the GI tract, suggested that the concomitant use of antacid and orange juice should be avoided in children. Other alternatives to the use of aluminum antacids include the use of calcium carbonate, magnesium compounds, or heteropolyuronic acid polymers in dialysis patients.[226,227]

B. ROLE OF PARATHYROID HORMONE AND VITAMIN D

In recent years, it has become apparent that the intestinal absorption and drug-induced effects of aluminum-containing compounds are related to the hormonal status of the infant. Potter et al.[173] demonstrated that in children undergoing CAPD there is a significant increase in serum parathyroid hormone levels. A similar elevation in serum parathyroid hormone was noted in children undergoing hemodialysis.[174] It is of interest aht administration of aluminum-containing drugs to dialysis patients resulted in an increase in both aluminum and parathyroid hormone levels in serum.[175] The finding that in conditions of normal kidney function in hyperparathyroid individuals there was an enhanced uptake of aluminum into the parathyroid gland following ingestion of this metal[176] further supports the suggestion that parathyroid hormone plays a role in aluminum pharmacokinetics. Mayor and Burnatowska-Hledin[177] demonstrated that parathyroid hormone enhanced the intestinal absorption of dietary aluminum in rats. Further, with the use of cultured mouse bone cells, aluminum was shown to inhibit collagen synthesis and depress cell proliferation.[231] These metabolic processes are dependent on parathyroid hormone, suggesting that aluminum interferes with the action of this hormone on bone cells.

It is well known that the actions of parathyroid hormone on mammalian bone mineral homeostasis are interrelated with the effects exerted by the prohormone, vitamin D. Potter et al.[173] demonstrated that in children with hyperparathyroid bone disease administered aluminum-containing drugs undergoing CAPD, the disease state became worse in the absence of vitamin D. In addition, aluminum was found to lower serum vitamin D levels.[220] Hence, vitamin D is utilized during dialysis in hyperparathyroidism to suppress parathyroid hormone secretion and prevent aluminum-induced osteomalacia.[177] However, Balfe et al.[178] found that despite vitamin D administration, the observed kidney osteodystrophy worsened during

TABLE 5
Summary of Tissue Distribution and Adverse Effects of Aluminum

Tissue sites	Ref.	Adverse effects	Ref.
Bone	184, 189, 190	Dialysis encephalopathy syndrome	166, 189, 248
Muscle	166		
Gray matter	166, 186	Microcephaly	194
Spleen	187	Microcytic anemia	196, 197
Liver	187, 191	Osteomalacic osteodystrophy	179, 201
		Developmental delay	224

CAPD in children with end-stage renal disease. The ineffectiveness of vitamin D therapy in children with aluminum-induced osteomalacic osteodystrophy has been reported by other investigators.[179,180] It has been suggested that the inability of vitamin D to counteract the parathyroid hormone-induced increase in aluminum absorption and accumulation in bone results in a vitamin D-resistant osteomalacia.[181,182] Evidence thus indicates that parathyroid hormone and vitamin D affect the intestinal absorption, tissue distribution, and eventual toxicity of aluminum.

C. FACTORS AFFECTING DISTRIBUTION IN BODY

The distribution of aluminum following oral administration of aluminum-containing phosphate-binding gels has been the subject of a number of investigations in an attempt to correlate metal accumulation with site of toxicity. In a number of adult patients on chronic hemodialysis receiving aluminum antacids to control serum phosphate levels, Parsons et al.[184] reported a rise in bone aluminum content. In an extensive study, Alfrey et al.[166] demonstrated that in uremic patients on dialysis administered aluminum phosphate-binding gels there was a significant increase in metal concentration in bone, muscle, and brain, particularly in the gray matter. It is of interest that in those individuals on dialysis who also developed an encephalopathy syndrome, a fivefold greater elevation in gray matter aluminum was noted as compared to patients on dialysis without this syndrome. In addition to bone and brain, large amounts of aluminum have been found to accumulate in spleen and liver in patients with renal failure.[187] In a subsequent study in a 2-year-old uremic child administered aluminum hydroxide orally to control hyperphosphatemia without hemodialysis, Nathan and Pedersen[186] found a significant elevation in brain aluminum at the time of autopsy at age 8 years. In addition to increased brain aluminum, a rise was noted in serum parathyroid hormone levels in this encephalopathic infant. Recently, Sedman et al.[188,189] demonstrated that in children with chronic renal failure receiving aluminum-containing antacids there was a marked increase in metal concentrations in bone biopsy specimens. It should be noted that even in the presence of normal kidney function, oral ingestion of aluminum antacids resulted in an accumulation of metal in bone tissue.[190] In infants and children on total parenteral nutrition with casein hydrolysate as protein source, Berquist et al.[191] found that aluminum accumulation occurred in hepatic tissue. Although the significance of aluminum accumulation in liver remains to be established, it was suggested that infants receiving total parenteral nutrition may develop cholestasis and hepatic fibrosis due to this metal.[191] Evidence thus indicates that aluminum body burden distribution is an important factor in the observed metal-inflicted clinical manifestations (Table 5).

At present, there is a concensus that the intestinal absorption of aluminum is related to the concentration of serum parathyroid hormone.[176,177] As the process of distribution is interrelated to absorption, the role of parathyroid hormone in tissue aluminum uptake has also been examined. In rats fed a diet supplemented with aluminum, Mayor et al.[175] found a significant metal accumulation in bone, kidney, muscle, and gray matter. However, if parathyroid hormone was injected to aluminum-fed rats, the concentration in these tissues rose two- to fivefold higher as compared to rats ingesting only metal. In a subsequent study, Mayor et al.[192] observed that the parathyroid hormone-stimulated increase in aluminum body burden was not apparently reversible upon withdrawal of the hormone. In humans, the tissue distribution of aluminum resembles that noted in the rat.[166,184,186] Hence, it has been proposed that both the intestinal absorption and tissue distribution of aluminum in man is also dependent on the concentration of parathyroid hormone.[177]

D. ADVERSE EFFECTS

The clinical manifestations of aluminum intoxication are well established and correlated with tissue body burden.[248] In adult patients undergoing dialysis, administration of aluminum antacids to bind phosphate produced an accumulation of this metal in brain gray matter and a disease called dialysis encephalopathy syndrome (DES).[166] Similarly, the use of aluminum hydroxide gel in infants and children with renal hypoplasia or chronic glomerulonephritis undergoing dialysis resulted in DES.[193] The neurological signs and symptoms in infants included ataxia, loss of motor abilities, myoclonus, seizures, dementia, and bulbar dysfunction, as well as a progressive slowing in the electroencephalogram. The phenomenon of DES in dialysis pediatric patients intoxicated with aluminum has been reported by several investigators.[171,189] However, recent studies have demonstrated that infants administered aluminum-containing phosphate-binding gels develop an encephalopathy even in the absence of dialysis.[188,194] In addition to symptoms seen in dialysis patients, Rotundo et al.[194] also found microcephaly, developmental delay, and hypotonia associated with aluminum use in nondialyzed children. The observation that encephalopathy can develop in infants with renal disease in absence of aluminum,[194] but that this syndrome is heightened when the metal is present, clearly indicates that the CNS of the infant may be highly susceptible to the neurotoxic effects of aluminum.[195]

The use of dialysate prepared from untreated tap water containing high levels of aluminum was attributed to result in microcytic, hypochronic anemia in adult hemodialysis patients.[196-198] Removal of aluminum from the dialysate led to a disappearance of the microcytosis and hypochromia, suggesting that this metal directly interferes with hemoglobin synthesis.[199,200] As in the case of adults, the use of a contaminated dialysate was associated with a microcytic and hypochromic anemia in children.[171,200] Although the source of parenteral aluminum remains a mystery, Sedman et al.[195] demonstrated that intravenous therapy in premature infants resulted in an accumulation of this element in bone. At present the severity of aluminum-induced microcytic anemia in premature infants is not known; however, these infants frequently require multiple transfusions to replace iatrogenic blood loss.[195] As the infant with a more rapidly developing skeletal system appears unduly susceptible to aluminum intoxication, the observed anemia in children may have more serious consequences. It is of interest that iron deficiency was not a causative factor involved in aluminum-induced anemia in children.[201] Further, the manifestations of aluminum-inflicted microcytosis and hypochromia were reversible.[171,200]

One of the prominent manifestations associated with the use of aluminum-containing phosphate-binding antacids is a syndrome called osteomalacic osteodystrophy. The characteristics associated with this disorder in adults include bone pain, multiple pathologic fractures, and myopathy in adult patients.[179,202] Histological examination of bone revealed a mixture of osteomalacia and fibrosis. In general, patients with aluminum-induced osteodystrophy tended to be refractory to vitamin D and displayed a hypercalcemia when small doses of calcitriol were administered. As expected in children undergoing CAPD, aluminum hydroxide gels were found to increase the osteoid surface and produce severe bone growth zone lesions, indices of a metal-induced osteomalacia.[169] Similarly, Andreoli et al.[211] demonstrated the presence of diffuse bony demineralization, fraying of the metaphyses of the long bones, osteopedia, pathological fractures of both femurs, severe osteomalacia, and reduced muscle strength in a child given aluminum hydroxide for hyperphosphatemia. Although the precise mechanism for aluminum-inflicted osteomalacia remains to be elucidated, Ott et al.[179] suggested that this metal may interfere with the process of bone mineralization. In a more recent study, Sedman et al.[219] demonstrated that aluminum impairs mineralization by a reduction in the number of osteoblasts, and this latter effect is distinct from inhibition of osteoid calcification. Since children administered aluminum-containing phosphate-binding antacids appear more susceptible to the development of bone disorders,[201] the observed osteodystrophy may have far more serious consequences, and the growth potential may be further compromised in the infant.[180] Indeed, Andreoli et al.[201] recommended that aluminum antacids not be administered to children with renal failure due to the action of this metal on brain, bone, and hematopoietic system.

Aluminum intoxication is known to produce osteomalacia characterized by abnormal osteoid. However, Ott et al.[179] recently described a bone lesion in patients in which osteoid width was normal, but the rate of bone formation was decreased. The aluminum-induced aplastic lesion in bone is accompanied by normal calcium levels without an elevation in parathyroid hormone. The aplastic form of aluminum intoxication thus differs from the more frequently reported osteomalacia type. In a subsequent study, Ott et al.[221] produced an aplastic bone lesion in young growing rats accompanied by no marked change in serum parathyroid hormone levels. It is of interest that upon cessation of aluminum administration, the aplastic lesion was reversible despite the continued presence of metal in bone. The effect of aluminum on bone formation and the reversibility of this phenomenon in human infants have not been resolved.

A potential source of aluminum for the fetus and newborn which has received virtually little attention is the lactational route. During pregnancy, dyspepsia is a common complaint and mothers tend to use antacids to reduce the adverse symptoms. Weberg et al.[213] demonstrated that low concentrations of antacids did not result in elevated serum aluminum levels in mothers and newborns. It was suggested that low-dose aluminum antacids failed to produce hyperaluminiumemia. However, the effects of high-dose antacids normally employed for peptic ulcer disease were not studied on the newborn. Despite the relative safety of low-dose antacids, Weberg et al.[214] recommended against high-dose antacids during pregnancy. This is supported by recent reports that administered aluminum to pregnant mice or rats throughout gestation produced no teratogenic alterations. However, the offspring of aluminum-fed dams displayed a decrease in body weight and crown pump length accompanied by a retardation in neurobehavioral development.[224,249] The interaction between aluminum antacids and other drugs has received little, if any, attention in the pediatric population. It should be noted that simultaneous administration of aluminum antacids and other drugs to adults altered the bioavailability of propranolol, procainamide, isoniazid, phenothiazines, digoxin, ranitidine, indomethacin, and tetracyclines.[231,232,242] Although Albin et al.[231] reported that aluminum did not markedly affect the bioavailability of prednisolone or cimetidine, a decrease was indicated by Steinberg et al.[234] In cases where aluminum is known or suspected to interfere with the bioavailability of other drugs, it was recommended that simultaneous administration be avoided. This recommendation would certainly apply in the therapy of children.

E. USE OF DEFEROXAMINE AS ANTIDOTE

The knowledge that the use of aluminum-containing phosphate-binding compounds in dialysis patients released aluminum which was subsequently implicated in the pathogenesis of neurological disorders, microcytic anemia, and bone disease prompted several investigators to search for an antidote to aluminum intoxication. Administration of deferoxamine to an adult patient undergoing hemodialysis, who developed DES, was found to chelate the aluminum in the individual and gradually resolve the neurological disturbances.[203] Prior to therapy, the patient developed epileptic seizures, myoclonic jerks, apraxia, and mutism, as well as inability to walk due to severe myopathy. However, with deferoxamine therapy, Ackrill et al.[203] found that this patient was free from these neurological symptoms and also walking normally. Similarly, in a patient undergoing CAPD who had been treated with aluminum hydroxide and developed encephalopathy, the administration of deferoxamine was shown to restore speech and behavior to a normal pattern.[204] It is of interest that the osteomalacia associated with dialysis, where aluminum levels are known to be elevated,[185] is also reversed by deferoxamine. The use of deferoxamine was also recently found to ameliorate the bone histology in uremic patients.[240] Brown et al.[205] observed in a dialysis patient the presence of multiple fractures and deformities. However, administration of deferoxamine decreased the depth and extent of the osteoid without a change in the deformity, suggesting that chelation effectively blocked dialysis-induced osteomalacia. Recently, in individuals undergoing hemodialysis who had received aluminum-containing antacids, Malluche et al.[206] demonstrated that deferoxamine decreased muscle and bone pain and lowered the volume of lamellar osteoid, and this was associated with a reduction in bone aluminum. Evidence thus suggests that aluminum-inflicted neurological and bone disorders can be effectively treated with chelation therapy in adults.[215] It should be noted that deferoxamine administered intraperitoneally or intramuscularly is as efficacious and safer than intravenous chelation therapy.[241]

In recent years, deferoxamine has been implemented as a tool to counteract aluminum intoxication in children. Although the number of trials is far less than in adults, the success rate is encouraging. In a 7-year-old boy maintained on CAPD and given aluminum hydroxide for hyperphosphatemia, the child developed a microcytic anemia; an osteomalacia characterized by a decrease in osteoid volume and bone and muscle pain, as well as pathologic fractures; and an encephalopathy with features such as myoclonic seizures, reduced scholastic performance, and an abnormal electroencephalogram.[201] Administration of deferoxamine to this child produced a resolution in the anemia and osteomalacia as well as improvement in the neurologic symptoms. Similarly, Warady et al.[200] and Freundlich et al.[207] each report separate cases in which a 2-year-old infant displaying the symptoms of aluminum intoxication is successfully treated with deferoxamine in that the chelating agents reversed microcytic, hypochromic anemia and osteomalacia, as well as improved the neurological disorder. It should be emphasized that even after deferoxamine therapy, Warady et al.[200] found that the infant continued to display delay in neurological development. These results suggested that although deferoxamine was capable of chelating aluminum, it would appear that the infant brain is more susceptible to aluminum intoxication and that chelation was not effective in reversal of all aluminum-induced neurological disturbances. The use of deferoxamine itself has been attributed to result in cataract formation, visual impairment, anaphylaxis, thrombocytopenia, hypotension, and abdominal pain.[208-210,239] However, the chelation of aluminum with deferoxamine did not appear to produce these adverse reactions.[206,207] In a recent study, renal transplantation was found to be effective in the treatment of aluminum-induced renal osteodystrophy in adults.[212] Data on the use of this therapeutic measure in children are currently not available.

Aluminum-containing phosphate-binding antacids are administered in pediatric nephrology to control hyperphosphatemia. The absorbed aluminum tends to distribute primarily in bone and gray matter of the brain. These tissue sites subsequently serve as the locations for toxic manifestations of aluminum in children. As a consequence, infant aluminum intoxication is characterized by osteomalacia, microcytic anemia, and an encephalopathy. Chelation of aluminum with deferoxamine can reverse osteomalacia and anemia and improve, but not restore to normal, the neurological symptoms in children. Hence, the use of aluminum-containing phosphate binders in children with chronic renal failure should be avoided wherever possible.[220,201] The Committee on Nutrition of the American Academy of Pediatrics recently reviewed the uses and toxicity of aluminum in infants and children. It was suggested that careful clinical and biochemical monitoring are warranted to establish the risk factor in children exposed to aluminum preparations, as dietary sources such as infant feeding formulas contain high metal levels which can attentuate the toxicity risk.[216]

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Chapter 16

IRON POISONING

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TABLE OF CONTENTS

I. Introduction 296

II. Toxic Effects of Iron 296
  A. Gastrointestinal Toxicity 296
    1. Apparent Improvement and Stability 296
  B. Circulatory Shock 297
  C. Hepatic Necrosis 297
  D. Gastric Scarring 297

III. Approaches to Management 298
  A. Triage 298
  B. Decontamination 300
    1. Laboratory Evaluation 301
  C. Chelation Therapy 301
  D. Supportive Care 302
  E. Other Resources 302

IV. Controversies in the Management of Iron Intoxication 303
  A. Intragastric Complexation 303
  B. Administration of Deferoxamine 304
  C. Gastrotomy for Tablet Removal 304
  D. Hemodialysis and Exchange Transfusion 305

V. Summary 305

References 305

I. INTRODUCTION

Iron-containing products remain a continuing toxicologic hazard to children. In the 1987 report of the American Association of Poison Control Centers' National Data Collection System,[1] 17,145 cases of acute iron ingestion had been reported to 63 participating regional poison centers involved in data collection. Data gathered by the statewide Arizona Poison Control System[33] show ferrous sulfate tablets and vitamins containing iron remain among the top ten substances ingested by children younger than 5 years of age. Widespread availability, the large number of tablets prescribed, a failure of parents and the general public to recognize the potential lethality of iron intoxication, and the failure of safety closures have all been suggested as contributors to the continuing risk of accidental ingestion of these products.[2] Despite the frequency of iron intoxication and the many articles suggesting various therapies for iron intoxication, the management and determination of severity during acute iron poisoning remains, for clinicians, an area of confusion and much controversy.

II. TOXIC EFFECTS OF IRON

The pathophysiology of iron intoxication was initially described by Covey in 1954.[3] The clinical features of this condition can be characterized by five stages:

1. Gastrointestinal (GI) toxicity,
2. Apparent improvement and stability
3. Circulatory shock
4. Hepatic necrosis
5. Gastric scarring

The time course, severity, and when these stages occur are related to the amount of iron ingested and the response to ongoing treatment.

A. GASTROINTESTINAL TOXICITY

The first obvious signs of toxicity in acute iron ingestions are gastrointestinal. These effects include vomiting, rapid onset of diarrhea, colicky abdominal pain, and GI hemorrhage. The mechanism of this toxicity is not clearly defined. Symptoms may appear as early as 30 min, but are usually present within 6 h following ingestion. In the routine absorption of dietary iron, the transport of ferrous sulfate involves a complex energy-dependent transport system. This saturable, carrier-mediated uptake process is dependent upon binding of iron in the lumen of the GI tract and is the rate-limiting step for iron absorption. Toxic amounts of iron in solution are rapidly absorbed in the large and small bowel in a concentration-dependent fashion, suggesting that a saturable transport system is not involved at high concentrations. Thus, in the acute overdose situation, it is presumed that the normal mechanisms of absorption have been exceeded and that absorption is a passive, first-order process.

Iron acutely and directly damages the GI tract. Histologically, the gastric and small intestinal mucosa appear to bear the burden of damage. Deposition of iron can be demonstrated in mucosal collagen and basement membranes and in cell nuclei and tissues of the vascular supply to the small bowel. Coagulative necrosis with platelet aggregation is observed at these sites. In many ways, there are stiking similarities in the amount and extent of damage that take place in the GI tract when acute iron and corrosive ingestion are compared. In the absence of frank hemorrhage, the GI effects of iron may lead to systemic hypovolemia by causing "third spacing" of fluid into the small bowel.[4]

1. Apparent Improvement and Stability

Given the acute effects of iron on the GI tract and the rapid loss of fluid volume, it seems unlikely that severe iron intoxication could be associated with an absence of obvious symptoms. This poorly described second stage of iron poisoning begins as early as 3 to 4 h after the ingestion, lasting as long as 48 h. Poor tissue perfusion, mild hyperventilation (secondary to acidosis), oliguria, and continued GI symptoms should suggest the presence of a severe ingestion. In cases of mild severity, recovery is complete with only supportive therapy given during the quiescent period. If the iron poisoning is moderate to severe, the patients's clinical status will worsen and the course quickly evolves into the third stage.

B. CIRCULATORY SHOCK

The third stage of iron poisoning is characterized by acute circulatory shock. The mechanisms of shock in iron poisoning are multifactorial and therefore treatment must be directed at correcting the various causes. These factors all contribute to profound hypovolemia and hypoperfusion, leading to shock. In animal models where this has been studied,[4,5] certain consistent factors have been found. Following the acute administration of lethal doses of ferrous sulfate, there is a dramatic decrease in circulating plasma volume, as reflected in increases in the hematocrit. Cardiac output is lowered on the basis of a decreased filling pressure. In addition to fluid losses, this decrease in effective filling pressure may be caused from metabolic acidosis and venous pooling by a direct loss of vascular tone.

An explanation given for the metabolic acidosis is it results from the conversion from the ferrous to the ferric ionic state following absorption. Studies have demonstrated that direct addition of iron in the ferrous state to blood may directly decrease bicarbonate.[6] The inhibitory effects of iron on complex oxidative metabolism at the cellular level may also result in increasing lactic acid concentrations.[6] Low cardiac output and high systemic resistance are the clinical presentations seen in the acutely iron-intoxicated infant. Such infants present in a tachycardic and extremely pale condition, with cold extremities and decreased central venous pressures.

The coagulopathy and resultant bleeding associated with iron intoxication may contribute to hypovolemia. The basis for this abnormality is probably secondary to hypoperfusion and intravascular damage. Free iron in the circulation inhibits the action of thrombin on fibrinogen and adversely affects coagulation.[7] Additional evidence points to a diminished ability to produce thrombin in the presence of high concentrations of iron.[8,9]

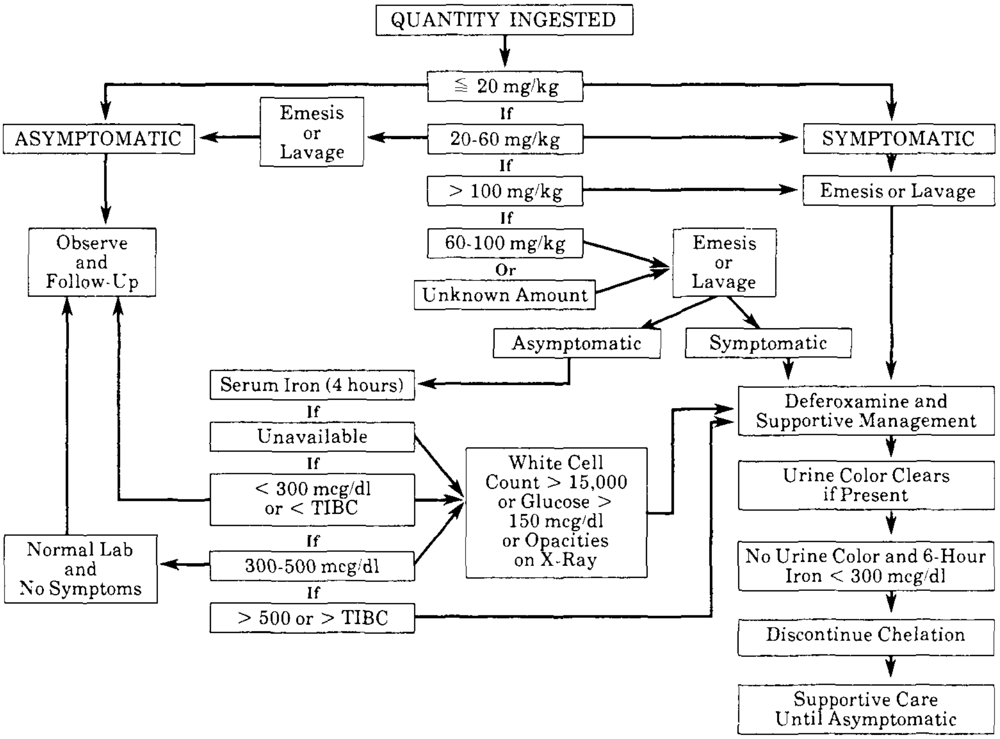
Shock from iron intoxication rquires early and aggressive treatment. Restoration of intravascular volume is critical before the effects of hypoperfusion and ischemia to tissue become irreversible. The need for prompt recognition of the intravascular volume status of the patient and the potential for GI hemorrhage and primary disturbances of coagulation make it imperative for the clinician to monitor more than simply blood pressure. By observing for tachycardia, poor perfusion of skin, oliguria, and acidosis, early intervention can be undertaken to reverse the progression of the adverse circulatory effects.

C. HEPATIC NECROSIS

During stage four, symptoms and findings are related to acute hepatic injury. The liver is a target organ for damage by direct uptake of iron in intoxication. Iron can be taken up directly by the reticuloendothelial system of the liver and spleen and it exerts a toxic effect on the mitochondria of the liver cell. Fatty degeneration mitochrondrial and portal injuries are changes seen in the liver. Fortunately, this is an extremely rare clinical manifestation of iron toxicity.

D. GASTRIC SCARRING

Following an acute corrosive insult to the GI tract, the healing process may result in areas of stenosis and stricture formation in both the stomach outlet and the small bowel. The late consequences of iron poisoning occur rarely. They may present as late as 2 to 6 weeks after the inciting event.


QUANTITY INGESTED
≦ 20 mg/kg
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If
> 100 mg/kg
If
60-100 mg/kg
Or
Unknown Amount
ASYMPTOMATIC
Emesis or Lavage
SYMPTOMATIC
Emesis or Lavage
Observe and Follow-Up
Emesis or Lavage
Asymptomatic
Symptomatic
Serum Iron (4 hours)
If
Unavailable
If
< 300 mcg/dl or < TIBC
If
300-500 mcg/dl
If
> 500 or > TIBC
Normal Lab and No Symptoms
White Cell Count > 15,000 or Glucose > 150 mcg/dl or Opacities on X-Ray
Deferoxamine and Supportive Management
Urine Color Clears if Present
No Urine Color and 6-Hour Iron < 300 mcg/dl
Discontinue Chelation
Supportive Care Until Asymptomatic

FIGURE 1. Steps to management of acute iron poisoning. (From Banner, W. and Tong, T. G., *Pediatr. Clin. North Am.*, 3, 402, 1986. With permission.)

III. APPROACHES TO MANAGEMENT

The large number of exposures to iron-containing products and the relatively infrequent mortality suggest that a wide range of severity exists in acute iron intoxication. Some guidelines must be used to assure the appropriate triage of the iron-intoxicated patient to provide an appropriate level of intervention. In addition, the appropriate use of laboratory tests and X-ray studies is demanded by restraints on treatment and hospitalization costs. The challenge involved with the management of iron poisoning is to recognize the severity of the occasion and to intervene by providing chelation therapy and supportive care in situations wherever indicated.

A. TRIAGE

Attempting to base protocols for triage on a single factor, such as the ingested dose, overlooks the complexities of human poisoning. A multifactorial approach to iron intoxication that includes the maximal estimated dose, the clinical status of the patient, and the serum iron level determination should be attempted. Figure 1 presents an algorithm for an approach to the triage of the iron-intoxicated patient.

Whenever calculating milligrams per kilogram doses of iron, it should be kept in mind that the *elemental* iron per dosage unit is only a small fraction of the total milligram weight of a capsule or tablet. Table 1 shows the amount of the elemental iron for a number of popular iron-containing products. Our approach is to always take into account the worst possible case whenever the milligrams per kilogram per dose is used to assess severity. When considering the number of possible tablets ingested, estimates of how full the bottle was or number of tablets previously used may yield misleading results. In general, we assume that the maximal number of tablets missing from a bottle is the amount that the

TABLE 1
Iron Content of Common Iron-Containing Products

Product	Total elemental iron per dosage unit (mg/tablet)
Ferrous sulfate, 325 mg	65 mg
Ferrous gluconate, 325 mg	40 mg
Ferrous fumarate, 325 mg	105 mg
Ferrous fumarate, 200 mg	66 mg
Chocks® plus iron	18 mg
Chocks Bugs Bunny® plus iron	18 mg
Feosol® elixir (sulfate)	44 mg/5 ml
Fergon® elixir (gluconate)	35 mg/5 ml
Fer-In-Sol® capsules (sulfate)	60 mg
Fer-In-Sol® drops	15 mg/0.6 ml
Fer-In-Sol® syrup	18 mg/5 ml
Filibon® capsules (fumarate)	30 mg
Flinstones plus iron	18 mg
Monster vitamins with iron (fumarate)	12 mg
Natabec (sulfate)	30 mg
Natalins® Rx (fumarate)	60 mg
Natalins® (fumarate)	45 mg
One A Day® plus iron	18 mg
One A Day® plus minerals	18 mg
Poly-Vi-Flor® drops with iron (sulfate)	10 mg/ml
Poly-Vi-Sol® drops with iron (sulfate)	10 mg/ml
Poly-Vi-Flor® tablets with iron (fumarate)	12 mg
Poly-Vi-Sol® tablets with iron (fumarate)	12 mg
Spider-man® vitamins with iron	18 mg
Stuart formula tablets (fumarate)	60 mg
Stuartinic® tablets (fumarate)	100 mg
Theragram M® tablets (carbonate)	12 mg
Tri-Vi-Sol® drops with iron (sulfate)	10 mg/ml
Unicap M® plus iron (sulfate)	10 mg
Unicap Plus Iron® (sulfate)	18 mg

From Tong, T. G. and Banner, W., in *Current Emergency Therapy — 1984*, Edlich, R. F. and Spyker, D. A., Eds., Appleton-Century-Crofts, Norwalk, CT, 1984, 754. With permission.

child has ingested. Determination of the estimated dose taken is the first step in the triage of iron intoxication. In those ingestions in which the maximal amount ingested is less than 20 mg/kg of elemental iron, there is generally little risk for toxicity and no specific treatment is indicated. In the 20- to 60-mg/kg range, we intervene by advising the use of syrup of ipecac and follow-up these children at home by telephone. The intent here is to decontaminate and limit the contact time of the iron in the GI mucosa. A conservative estimate of more than 60 mg/kg of elemental iron should be an indication for medical evaluation. It should be kept in mind that these milligrams per kilogram amounts taken are intended only for use as guidelines in children younger than 5 years of age who have acutely ingested an unknown quantity of iron. Adolescent and adult overdoses should be viewed as intentional and require immediate medical referral regardless of the estimated dose taken. In addition, injury to the GI tract from large amounts of iron ingested by the older child or adult may occur, even though the total body burden of iron is not considered to be in the toxic range.

The clinical status of the patient is an important indicator of whether there is a need to initiate aggressive management in iron poisoning. In situations in which a patient becomes symptomatic, particularly with early GI symptoms, such as spontaneous emesis, epigastric pain, and diarrhea, referral to a treatment facility is appropriate even if the estimated amount taken is low. In cases where lethargy, hypotonia, hypoperfusion, tachypnea, and tachycardia are seen, immediate chelation therapy is indicated regardless of the amount of iron reportedly ingested.

The serum iron level is another major determinant in the decision to institute aggressive therapy in cases of iron intoxication. The utility of serum iron determinations has been a source of controversy for many years. Critical to an understanding of the use of serum iron concentrations is an appreciation of the role of the total iron-binding capacity (TIBC). The iron-binding proteins in serum are regulated physiologically, but generally allow 200 to 300 μg/dl or iron-binding capacity. In theory, iron toxicity is more likely to occur when the serum iron concentration exceeds the ability of plasma proteins to bind it. In practice, however, the correlation between toxicity and iron-binding capacity appears to be relatively poor. The iron-binding capacity primarily measures a high-affinity binding site. Lower binding affinities may be present, as well as rapid transfer to iron-binding sites in liver and tissue that can remove free iron from the circulation. Occasionally, unusual results of TIBC may occur. Thus, the use of TIBC may occasionally be unreliable in severe iron intoxication.

It is also important to consider the impact of timing on the collection of serum iron concentrations. Because iron undergoes multicompartment kinetics with a fairly rapid distribution phase followed by an extremely long terminal elimination phase, dramatic chagnes in serum concentration may occur within the first few hours following ingestion. In addition, variable disintegration time of the tablets and capsules may also alter serum iron concentration-time relationships. Because of these factors, we have generally tired to measure serum iron concentrations between 4 and 6 h postingestion. During this time, the majority of oral iron preparations will have solubilized and serum iron will not yet have undergone complete distribution into tissue.

Iron concentrations in excess of 1000 μg/dl are associated with a dramatic increase in morbidity.[10] In addition, an unacceptable risk of shock is present (20%) when serum iron concentrations exceed 500 μg/dl. Thus, there is very little argument that a serum iron concentration greater than 500 μg/dl strongly supports the need for aggressive therapy.

Serum iron concentrations that fall between 300 and 500 μg/dl are often the greatest source of confusion. Our recommendations for patients with serum iron determinations in this range have been to begin chelation therapy if the iron concentration exceeds the TIBC (when available) or if the patient is experiencing any of the signs and symptoms of iron toxicity. The white blood cell count and serum glucose may be used as further indicators of systemic toxicity.[11] An abdominal radiograph should also be obtained in order to determine whether a large mass of tablets remains to be absorbed. Solid dosage forms of iron are sometimes evident on X-ray 6 to 8 h following their ingestion. As dissolution of tablets and capsules containing iron takes place, discrete forms may not be easily discerned; amorphorous densities may appear instead. Solutions and suspensions at high concentrations of iron, however, may be visualized.

It should be obvious that no single laboratory value or single historical or physical finding should be used as evidence to withhold therapy. Even when there are "normal" serum iron concentrations, it is reasonable to initiate chelation therapy in patients who are manifesting major clinical signs of toxicity. A negative X-ray examination does not alone rule out the possibility of severe poisoning from disintegrated iron tablets. By taking the approach of using the estimated total body burden of elemental iron, clinical signs and symptoms, and the serum iron concentration, a more rational approach to the initiation of chelation therapy can be undertaken.

B. DECONTAMINATION

The use of syrup of ipecac and gastric lavage in clinical toxicology situations is usually a relatively straightforward discussion. For iron intoxication, however, there is some controversy and confusion on this issue. Based on our own case experiences, we offer the following recommendations:

1. Basic gastric decontamination procedures should be undertaken with as little delay as possible. The use of syrup of ipecac as an immediate measure in the home or during transportation to a treatment facility is a reasonable approach in the awake and alert child. It may be desirable to additionally lavage a child once the hospital or other medical setting has been reached, especially if the quantity of ingested iron is reportedly large. Any time delay in the initiation of decontamination procedures to await specific chelating or complexing agents is unacceptable.
2. The use of complexing or chelating agents is unnecessary in the initiation of gastric lavage, because it is primarily a mechanical procedure to remove substances from the stomach.
3. Complexation with phosphate solution should be avoided.
4. The use of conventional antacid preparations or 5% sodium bicarbonate may be useful in complexing iron and decreasing the corrosive effects of stomach acid upon a denuded gastric mucosa.
5. There are not data to support the use of intragastric deferoxamine, and we have chosen to avoid this approach.
6. Activated charcoal is not effective for complexing residual iron in the gastrointestinal tract.

Following gastric decontamination, abdominal radiography may be useful to identify large masses of iron still intact in the GI tract. The finding of multiple or amorphous densities in the stomach requires that additional attempts at removal be understaken. Only in rare circumstances in which a large number of densities are apparent and attempts at alternate GI decontamination have failed would surgical removal be indicated. If surgical intervention is contemplated, radiography immediately prior to operation is mandated to ensure that tablets or capsules have remained in one location.

1. Laboratory Evaluation

Laboratory evaluation in acute iron intoxication should be directed toward those tests that will aid in the diagnosis and delivering of supportive care. Once the initial serum iron has been determined to be in the toxic range, there is little value to continued determinations of the serum iron or TIBC. In many institutions, the TIBC cannot be determined on an immediate basis; therefore, it becomes of relatively little value in monitoring therapy. In cases of severe GI toxicity due to iron, it is wise to obtain a hematocrit and cross-match for blood products if hemorrhage occurs. Additional baseline laboratory tests may include a white blood cell count and serum glucose determination to assess the level of acuity of the patient. An arterial blood gas or bicarbonate determination is important in monitoring the development of metabolic acidosis. Serum calcium and coagulation studies are also useful in severe intoxications; these may become abnormal. Determination of serum electrolytes is useful in the overall fluid management of the patient. There is little value in obtaining indicators of hepatic function early in the course of iron intoxication; however, it is reasonable to obtain transaminase determinations after the first 24 h to assess whether or not hepatic damage has occurred.

C. CHELATION THERAPY

Deferoxamine should be initiated intravenously by continuous infusion in all cases of serious iron poisoning. We recommend a slow continuous intravenous infusion of deferoxamine (deferoxamine should never be given rapidly), starting with a dose of 15 mg/kg/

h. Some authors recommend decreasing the rate to 6 mg/kg/h after the first 4 to 5 h of chelation therapy. Chelation therapy at 15 mg/kg/h should be continued while evidence of the iron-deferoxamine complex in the urine is seen.[12] A major exception to the use of intravenous deferoxamine is when prolonged interhospital transport time is involved. If close monitoring of intravenous infusions is not possible, it may be more judicious to give deferoxamine by the intramuscular route. Intramuscular administration of deferoxamine is painful and often responsible for local reactions at the injection site. Adverse effects of deferoxamine therapy include hypotension and tachycardia following too-rapid infusion; urticaria and erythema have also been noted.

The decision to discontinue chelation therapy should be made on the basis of several parameters. Traditionally, a change in urine color from normal to ''vin rose'' has been interpreted as an indication for continued chelation therapy. Observation in which a high concentration of chelated iron was present in urine without changes in color has been reported.[13] Thus, in a situation in which the serum iron concentration is well above 500 μg/dl and no change in urine color is observed, it is reasonable to continue chelation therapy until the serum iron has fallen to less than 300 μg/dl. In those patients with serum iron concentrations in the 300 to 500 μg/dl range and even when the TIBC is exceeded, frequently no change in urine color will occur during chelation. In most patients in whom the traditional ''vin rose'' color does occur, it is suggested that chelation therapy continue until a normal urine output of normally colored urine occurs. When the urine color has cleared, continuing chelation for an additional 24 h or stopping it immediatley have both been suggested. This decision should be based on the assessment of severity.

D. SUPPORTIVE CARE

Supportive care is the singular and most important mode of management of the iron-intoxicated patient. Initial attempts should be made to minimize the impact of iron tablets on the GI tract and to monitor for the presence of GI hemorrhage. With the fluid loss in the GI tract and the generalized loss of capillary integrity in the body, the most important factor in supportive care is to sustain the intravascular volume. Elevation of the hematocrit in iron intoxication is an important indicator of fluid volume loss and should be dealt with aggressively. Monitoring of urine output, heart rate, and assessment of tissue perfusion along with measurement of the central venous pressure should guide fluid therapy. Large fluid volumes may be needed during the first 24 h of management in order to avoid the risks of hypovolemic shock. In addition, correction of acidosis and hypocalcemia and monitoring of serum electrolytes are important in the management of iron intoxication.

E. OTHER RESOURCES

Chelation of iron with deferoxamine is a relatively ineffective way of binding large amounts of iron. The amount of iron removed from the body during chelation is a relatively small percentage of the total body burden of iron. Recommendation that deferoxamine be given until either a maximum 24-h dose of 6 g or 240 mg/kg is reached is not supported well with current data. As 1 g of deferoxamine chelates only 85 mg elemental iron, this maximum dose recommendation may be insufficient to neutralize the iron taken in large overdoses. When serum iron concentrations are markedly elevated, some have suggested the use of exchange transfusion.[14] From a toxicokinetic standpoint, if iron has remained in the intravascular compartment as evidenced by serum concentrations greater than 5000 μg/dl, there may be some advantages to exchange transfusion under these rare circumstances. There are no data to suggest that the routine management of acute iron intoxication requires this kind of intervention. Hemodialysis may effectively remove the complex of deferoxamine and iron, but is considered to be a less efficient method for removal than is glomerular filtration. Hemodialysis is rarely suggested unless renal failure has occurred. The vast majority of iron intoxications will respond to standard intravenous chelation plus good supportive measures and will unlikely require more aggressive therapy.

IV. CONTROVERSIES IN THE MANAGEMENT OF IRON INTOXICATION

As with many toxicologic issues, the inability to perform well-controlled prospective studies has led to a great deal of confusion and controversy in the management of the iron-intoxicated patient. Conflicting suggestions and lack of consensus on management provide a continuing source of difficulty for the clinician. Recognizing that this area is controversial, the clinician must use his or her judgment in deciding the most rational course for an individual patient. It is important to recognize that some procedures such as gastrotomy, although not useful for the vast majority of patients, might be beneficial in a minority of patients. The role of the clinician remains to balance the risks and benefits for his or her patient.

A. INTRAGASTRIC COMPLEXATION

The use of intragastric complexation in iron intoxication is one ongoing controversy. Sodium bicarbonate and phosphate solution have been suggested to promote the formation of insoluble iron complexes.[11,15] Studies have demonstrated that phosphate can decrease iron absorption in normal human subjects, but fail to address the same issue in iron intoxication. Sodium bicarbonate and sodium phosphate will form relatively water-insoluble iron complexes in the stomach when given orally.[16] These complexes are labile, and a subsequent decrease in pH into the normal range of gastric fluid can allow iron to again become soluble.

There seems to be little advantage in using either of these solutions during the mechanical lavage of the stomach. When normal saline is introduced into the stomach, it is hardly relevant whether the material to be removed by lavage is in a soluble or insoluble form. The more important question is whether the residual iron that is not effectively removed by lavage or emesis can be maintained in an insoluble state for a prolonged period of time, thus making it less absorbable. Sodium bicarbonate administered in sufficient quantities to maintain the GI environment in the desired pH range would require repeated doses, which may result in rises in serum sodium. In the case of phosphate-containing solutions, the amount of phosphate absorbed from the use of this as a lavage solution during iron intoxication has been shown to be hazardous.[17,18] Hypocalcemia, hyperphosphatemia, severe acidosis, and hypernatremia have occurred as a consequence of repeated and indiscriminate use of phosphate solutions. Several clinicians have advocated the use of magnesium hydroxide or Milk of Magnesia® to decrease the solubility of iron.[19] Clinical trials on the effectiveness of magnesium hydroxide in humans are still needed. With an iron-damaged stomach, it seems reasonable to protect the stomach and upper duodenum from further damage from stomach acids. To this end, the administration of conventional antacid preparations with low bioavailability for their buffering ions seems to present a useful and safe alterntive to the previously recommended therapies. To avoid iatrogenic complications, however, it should be remembered that magnesium-containing antacids may lead to increases in serum magnesium if renal function is impaired.

The use of deferoxamine as an intragastric chelating agent has received a great deal of discussion in the literature. The relevant considerations in intragastric chelation of iron with deferoxamine include:

1. Does complexation decrease the absorption of iron?
2. Does intragastric complexation decrease the toxicity of iron following absorption?
3. Is the intragastric administration of deferoxamine associated with any adverse effects?

Unfortunately, very few studies have been designed to directly address these questions.

Studies addressing the question of bioavailability of the iron-deferoxamine complex have failed to provide useful information for the management of iron intoxication. When deferoxamine is used orally in chronic iron overload states, the bioavailability of iron is decreased.[20,21] However, in animal studies of acute iron overdose, the iron-deferoxamine complex is absorbed.[22]

The question whether iron absorbed as the iron-deferoxamine complex is less toxic than iron absorbed alone and subsequently chelated with intravenous deferoxamine is more difficult to answer. It has been postulated that iron when absorbed as the complex may be less toxic because of its lower volume of distribution.[23] Under these conditions, distribution into cells and thus effects on the mitochondria could be avoided.

The potential adverse effect of intragastric deferoxamine is that it might somehow increase the rate of dissolution or increase the rate of absorption associated with acute iron ingestions. Evidence for this possibility comes from studies which show the biochemical parameters of iron toxicity associated with combined therapy of intravenous and oral deferoxamine appeared to progress more rapidly than those associated with intravenous deferoxamine alone.[22] Other investigators have found that concentrations of iron in the liver were increased in the presence of deferoxamine in the GI tract.[24]

As in the case of sodium bicarbonate, it seems irrelevant which fluid is used for mechanically washing out the stomach. Thus, it would appear to be an expensive approach to use deferoxamine merely as a lavage fluid. In addition to cost, only a limited supply of deferoxamine is usually available to the clinician in many rural practice settings.

B. ADMINISTRATION OF DEFEROXAMINE

The administration of deferoxamine as an intramuscular preparation is open to much discussion. Intramuscular or subcutaneous use of deferoxamine has been advocated for patients with chronic iron overload, such as those receiving repeated blood transfusions. Adverse effects noted with the use of deferoxamine by either the intramuscular or intravenous route are few.[25] The most stiking difference between intravenous and intramuscular deferoxamine is the effect of a rapid bolus of intravenous deferoxamine on blood pressure. This acute hypotension produced is most likely caused by the release of endogenous histamine.[26]

In cases of severe iron intoxication, it is difficult to recommend intramuscular medications when poor tissue perfusion is a primary complication early in the intoxication. Deferoxamine used as a continuous intravenous infusion at 15 mg/kg/h has been demonstrated to be safe and not associated with hypotension. One difficulty with current recommendations for the use of intravenous deferoxamine is the lack of agreement on maximal infusion rates.[12] Some have suggested initiating therapy with an infusion of 15 mg/kg/h and then decreasing this rate of infusion to 6 mg/kg/h after stabilization. The intravenous access can also be used conveniently to provide volume expansion should it be necessary as is often the case in severe iron intoxication.[27]

Deferoxamine administration in iron overdose may be accompanied by an increased risk for developing *Yersinia enterocolitica* septicemia. Case reports of this unusual infection postulate that deferoxamine, a siderophore, is acting as a growth factor *in vitro*, enhancing the virulence of the pathogen.[28]

C. GASTROTOMY FOR TABLET REMOVAL

Two recent reports have described the surgical removal of iron tablets from the GI tract following severe iron intoxication.[29,30] The indication for surgery used in both of these circumstances was the abdominal radiograph. When a large number of opacities are identified in a single location, it may be reasonable to consider surgical intervention. No real estimate of the risk-benefit relationship for this approach is known. The clinician must consider the stability of the patient, the number of tablets seen on radiograph, and the potential for other procedures such as lavage, emesis, and catharsis to successfuly remove these tablets. The propensity from some iron tablet preparations to form concretions may mandate this approach. Surgical intervention should be considered only if a large number of tablets inaccessible to emesis, lavage, or gastroscopy appear to be present, and the clinician should obtain radiographs immediately prior to surgical intervention. Laparotomy to remove iron concretions should not be considered a routine measure in iron intoxication.

D. HEMODIALYSIS AND EXCHANGE TRANSFUSION

As with many forms of intoxication, hemodialysis has been investigated in iron intoxication. It does appear that the complex of deferoxamine and iron can be removed by dialysis.[31] When confronted with the possibility of renal failure, this seems a reasonable approach; however, there appears to be relatively little advantage to the initiation of hemodialysis in cases in which renal function is normal.

Exchange transfusion is another area of controversy for many intoxicated states. Currently, recommended doses of deferoxamine will chelate very little of the total body burden of iron in a serious overdose. Exchange transfusion has been demonstrated to increase the rate of iron removal by as much as 30-fold when compared with chelation therapy alone in animal studies.[14] This approach should only be seriously considered in situations where other conventional therapies have failed and where serum iron concentrations are extremely high. Given the poor affinity of iron for charcoal, the use of charcoal hemoperfusion would offer little benefit, if any. Since the iron deferoxamine complex does bind to charcoal, further study and experience may suggest that this is a possible therapeutic approach.[30]

V. SUMMARY

Iron poisoning is a major toxicologic problem. Failure to recognize the severity of iron intoxication may result in an inappropriate level of intervention. Estimates of the total body burden of iron, clinical symptoms, and the serum concentration are needed before an appropriate decision can be made to initiate therapy. In severe intoxication, the use of intravenous deferoxamine is indicated, along with supportive care and particular attention given to maintaining the intravascular volume. Other measures should include correction of metabolic acidosis and disorders of coagulation. Replacement of blood components is necessary when there is evidence of GI hemorrhage. Measures such as hemodialysis and exchange transfusion should be reserved for those unusual poisonings in which more conventional therapy has been unsuccessful. In rare cases of iron intoxication, late sequelae such as hepatic necrosis and GI scarring with obstruction may occur. The prompt recognition and initiation of management of children with acute iron poisoning is the single most critical element in decreasing the morbidity and mortality associated with these products.

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INDEX

A

Acetamide, 156
Acetaminophen
  breast milk excretion of, 245
  fetal effects of, 7
  mechanism of action of, 243—244
  metabolic pathways of, 244
  toxicity of, 244—245
Acetazolamide, 4, 146
Acetylators, slow, 134
Acetylcholine, 252
N-Acetyl-β-glucosaminidase (NAG), 176—177
N-Acetylcysteine (NAC), 244, 296
N-Acetyl procainamide (NAPA), 83—84
Acrolein, 198
ACT-D, 202—203
Actinomycin-D, 202—203
Action potential durations (APD), 80, 87
Adrenalin, see Epinephrine
β-Adrenergic agonists, fetal effects of, 4
Adrenergic inhibitors, 132—133
Adrenergic receptors, 52—54
β-Adrenergic receptors
  agonist binding to, 53
  decreased density of, 53
  dobutamine and, 66
  downregulation of, 52—53
  epinephrine stimulation of, 56
  stimulation of, 57
Aglycones, 26
Alcohol, fetal exposure to, 2—3
Aldosterone, secretion of, 267
Aldosteronism, 124
Alkenes, activated, 27
Alkylating agents, 45, 192—199
Alkyl sulfonate, 196—197
Allergic disorders, antihistaminic agents for, 253—254
Allopurinol, 190
Allosteric effectors, 26
Aloe, 7
Aluminum
  chelation of, 285—286
  intestinal absorption of, 281
  sources of, 280
  tissue distribution and adverse effects of, 282—286
Aluminum antacids, 280
  adverse effects of, 283—284
  antidote to, 284—286
  factors affecting body distribution of, 282—283
  parathyroid hormone and vitamin D role in, 281—282
  pharmacokinetics of, 280—281
Aluminum hydroxide, 282
Amantidine, 4
Amenorrhea, 211
Amides, 24
Amikacin, 177—182
Amiloride, 132
Aminoglycosides
  adverse effects of, 175—178
  indomethacin and, 247
  clinical pharmacology of, 174—175
  low therapeutic index of, 181
  nephrotoxicity of, 175—177
  ototoxicity of, 177—178
  protein binding of, 174
  transplacental passage of, 174
Aminophylline, 4
Aminopterin, 4
Amiodarone, 96
  adverse effects and toxicity of, 98
  with digoxin, 105
  drug interactions of, 98
  electrophysiology of, 96—97
  with flecainide, 94
  pharmacokinetics and dosages of, 97
  quinidine and, 82
  treatment of overdose of, 98
  use of in pediatrics, 97
Amphetamines, 8
Amphiphilic drugs, toxicity of, 11
Amphotericin B, 175
Anaphylaxis, treatment of, 57
Androgens, 4
Angiotensin-converting enzyme inhibitors, 134—135
Anthracyclines, 199, 200
Antiarrhythmic agents, classification of, 78
Antibiotics, 199—203
Anticoagulants, 95, 102
Anticonvulsants, 102
Antidysrhythmic drugs, see also specific drugs
  class 1A, 79—86
  class 1B, 86—93
  class 1C, 93—96
  class II, 96
  class III, 96—99
  class IV, 99—103
  classification of, 77—78
  number, age distribution, and severity of intoxications of, 79
  toxicity of, 77
  used in pediatrics, 77—106
Antihistamine drugs, 259—260
  adverse effects of, 258—259
  chemistry of, 252
  classification of, 253
  pharmacokinetics of, 256—258
  pharmacological actions of, 252
  route of administration and intoxication with, 259
  therapeutic uses of, 253—254
    allergic disorders in, 253—254
    for asthma, 255
    for common cold, 256
    for otitis media, 255—256
    for vomiting and pregnancy, 254—255
Antihypertensive medications, 128—136, see also specific agents
Anti-L-asparaginase IgG antibodies, 206

Antimetabolites, 2, 187—192
Antineoplastic agents, 37—38, 199
Antineoplastic chemotherapy, toxicity of
  alkylating agents, 194—201
  antibiotics, 201—205
  antimetabolites, 189—194
  enzymes, 207—209
  hormones, 209—211
  miscellaneous, 212—215
  plant products, 205—207
Antiproliferative drugs, 46
Antiprostaglandin agents, metabolism and toxicity of, 242—247
Antipsychotic agents, 95
Apgar ratings, 255
Aplastic anemia, 165
Apnea, idiopathic, or prematurity, 235—236
Ara-C, 191—192
Aromatic nitro groups, 23
Aryl amine derivatives, 164
Aseptic bone necrosis, 208
Ask-Upmark kidney, 125
Asparaginase, 205—207
L-Asparagine synthetase, 206
Aspirin, 242—243
Asthma, treatment of, 57, 255
Atenolol, 129, 132
Atrioventricular (AV) block, 98
Atrioventricular (AV) node conduction, 83, 84
Atropine, 4, 106
Autocoid histamine, 252
Azathioprine, 4
Azopsermia, 211

B

Bactericidal antibiotics, 159
Bacteroides fragilis, 159, 168
Barbiturate blisters, 226
Barbiturates, 224, 229
  vs. benzodiazepines, 222
  chloramphenicol and, 168
  classification of, 225
  CNS stimulation by in children, 11
  hepatic biotransformation of, 225
  manifestations and treatment of intoxication with, 225—227
  pharmacology and pharmacokinetics of, 224—225
BCNU, 197—198
Bendectin, 254
Benzo(a)pyrene (BaP), 19—20
Benzo(a)pyrene 4,5-oxide, 24
Benzodiazepines, 222, 229
  pharmacology and phramacokinetics of, 222—223
  plasma concentrations of, 275
  toxicology of, 223—224
5,6-Benzoflavone, 24
Benzothiadiazines, 128
Benztropine, 269—270
Beta-adrenergic blockers, 96, 102, 132
Betadine (Povidone-Iodine), 7
Beta-lactam antibiotics, allergic reactions to, 168
β-Microglobuluria, 181
Bioactivating reactions, 30
Bioassays, 159
Biotransformation, see Drug biotransformation
Bleomycin, 200—202
Blood chemistries, 124
Blood pressure, age-specific percentiles of, 119—121
Bone marrow aplasia, 164
Bone marrow suppression, 165
Bradycardia, 100—103
Brain, 3, 40—41, 43—46
Breast feeding, drug exposure through, 6—7
Breast milk, 9, 243, 245, 247, 279
Bretylium, 98—99
Bromides, 4
Brompheniramine, 255, 257
Bronchodilation, β-adrenergic-mediated, 56—57
Bronchodilators, 255
Bronchopulmonary dysplasia (BPD), 142, 144—14 147
Bumetanide, 129
Bupivacaine, 4, 87
Busulfan, 4, 196—197

C

Caffeine, 7
Calcium antagonists, 101
Calcium channel blockers, 99—100
  with digoxin, 105
  dosages of, 101—102
  drug interactions of, 102
  electrophysiology of, 100—101
  with encainide, 95
  for hypertension, 135—136
  for hypertensive crisis, 126
  pharmacokinetics of, 101
  toxicity of, 102—103
Calcium chloride, 103
Captopril, 129, 134—135, 148
Carbimazole, 4
Carbon dioxide tension, 234
Carbonic anhydrase, 43
Carbon monoxide, 3
Carbon monoxide diffusing capacity (DLCO), 201—202
Carboplatin, 213
Carboxylic acid esters, 24
Cardiac conduction system, digoxin effects on, 103—104
Cardiac dysrhythmias, 94, see also Dysrhythmias
Cardiac glycosides, 79, 105
Cardiac index, 54
Cardiogenic shock, 60, 64
Cardiomyopathy, reversible, 166
Cardiopulmonary arrest, 56
Cardioquin, 81
Cardiovascular system, 54, 235
Cardiovascular surgery, dobutamine following, 67

Catecholamines, see also specific forms
  adrenergic receptors for, 52—54
  chemical structure of, 51
  decreased vascular sensitivity to, 53
  endogenous, response of, 54—56
  ontogeny of cardiovascular function and, 54
  pharmacodynamics of, 51—52
  pharmacokinetics of, 50—51
  pharmacology of specific types of, 56—67
  preparation of infusions of, 59
  uses of, 50, 58
CDDP, 212—213, see *cis*-Diamminedichloroplatinum II
Cell death, programmed, 46
Cell differentiation, 37, 46
Cell proliferation, 37, 44, 46
Central nervous system, see also Brain; Nervous system
  altered development of, 3
  antihistaminic effects on, 252, 258
  cimetidine toxicity in, 276
  methotrexate effects on, 189
Cerebral cortex, formation of, 44
Cerebrospinal fluid (CSF), 43, 161, 188
Charcoal hemoperfusion, 167, 227—228, 305
Chelation therapy, for iron toxicity, 301—302
Chemotherapeutic agents, 187
Chemotherapy, antineoplastic, 187—213
Children
  accidental poisonings of, 8, 12
  drug therapy in, 8
CHIP, see *cis*-Dichloro-*trans*-dihydroxybis(isoprophylamine) platinum
Chlorambucil, 4
Chloramphenicol, 156
  absorption and bioavailability of, 160—161
  antimicrobial activity of, 157—159
  assay methodologies for, 159
  chemistry of, 156
  current indications for clinical use of, 168
  distribution of, 161
  dosing of, 167—168
  drug interactions with, 168
  excretion of, 163
  fetal effects of, 4
  half-life of, 163—164
  hepatic dysfunction and, 163—164
  mechanism of action of, 156
  metabolic pathways of, 162
  metabolism of, 162—163
  metabolites of, 162—164
  pharmacokinetics of, 169
  protein binding of, 161
  renal dysfunction and, 164
  shock and, 164
  therapeutic monitoring of, 168
  toxicity of, 164—167
Chloramphenicol base, 160
Chloramphenicol monoglucuronide, 162
Chloramphenicol palmitate, 157, 160
Chloramphenicol sodium succinate, 157
Chloramphenicol succinate, 160—161, 168
Chlordiazepoxide, 4
Chloroquine, 4
Chlorpheniramine, 253, 255, 256
Chlorphentermine, 11
Chlorpromazine, 4
Chlorpropamide, 4
Chlorthaladone, 128
Chlorthiazide, 128
Cholestasis, 213
Choroid plexuses, 43
Chronic heart failure, dobutamine and dopamine in, 64—65
Cigarettes, fetal exposure to, 3
Ciliary epithelium, 39—40, 43, 46
Ciliary processes, 39
Cimetidine, 272, 274
  adverse effects of 275—276
  bioavailability of, 273—274
  with encainide, 95
  fetal effects, 4
mechanisms of action of, 274—275
  pharmacokinetics of, 272—274
  ranitidineand, 278—279
  therapeutic uses of, 275
Circulatory shock, 51, 297
Cisplatin, 46
  adverse effects of in chick embryo, 38—41
  chemical nature and mechanism of action of, 38
  cytotoxicity of, 38
  effects of on chick embryo, 36—46
  experiments using, 37—38
  mechanisms involved in prenatal brain lesions with, 43—45
  mechanisms involved in microphthalmia with, 41—43
Cisplatinum, 211—213
Clomiphene, 4
Clonidine, 129, 132—133
Clorazepate dipotassium, 222
Coagulation disorders, 245
Coagulative necrosis, 297
Cocaine, 8
Codeine, 7
Coloboma, 42—43, 46
Colorimetric assays, 159
Common cold, treatment of, 256
Congestive heart failure, 142—143, 149—150
Conjugation reactions, in perinatal period, 25—29
Conjunctivitis, 192
Corticosteroids, 207
  fetal effects of, 4
  gastroduodenal ulceration with, 273
  pharmacology of, 207
  toxicity of, 208—209
Cortisol, 207
Coupling proteins, 53
CTX, see Cyclophosphamide
Cyclic AMP, isoproterenol-induced, 53
Cyclizine, 4
Cyclophosphamide, 4, 42, 194—195

Cyproheptadine, 253
Cystic fibrosis, 272
Cystitis, hemorrhagic, 196
Cytarabine, 4
Cytosine arabinoside, 191—192

D

Dacarbazine, 198, 199
Dactinomycin, 202
Daunomycin, 199—200
Deferoxamine, 284—286, 301—304
Degenerative processes, types of, 45
O-Demethly encainide (ODE), 95
Deoxyribonucleotides, 210
Desmethyldiazepam, 222
Developmental stages, 2, 3, 42
Dexamethasone phosphate, 199
Dextromethorphan, 7
Dextropropoxyphene, 4
Dialysis encephalopathy syndrome (DES), 282, 283
cis-Diamminedichloroplatinum II, 211—212
Diazepam, 4
Diazoxide, 4, 10, 126
cis-Dichloro-*trans*- dihydroxy-bis(isoprophylamine) platinum (CHIP), 213
Diet, in hypertension management, 127
Diethylstibestrol, 2, 4
Digibind, 106
Digitalis glycosides, 104, 106
Digoxin, 103
  diltiazem and, 102
  drug interactions of, 105
  ECG manifestations of, 105—106
  electrophysiology of, 103—104
  with encainide, 95
  with flecainide, 94
  with furosemide, 148
  nifedipine and, 102
  organ distribution of in adults vs. infants, 10
  pharmacokinetics and dosing, 104—105
  quinidine and, 80—82
  toxicity of, 106, 247
  verapamil and, 102
Dihydrofolate reductase, 187—188
Dihydrotestosterone, 278—279
Diltiazem, 100—102, 135
Diphenhydramine, 7, 256—257
Disopyramide, 85—86, 102
Diuresis, for barbiturate intoxication, 226
Diuretics, 128—129
  with encainide, 95
  loop, 129—132, see also specific agents
  pharmacology and toxicology of in pediatrics, 142—150
  potassium-sparing, 132
  side effects of, 128
  thiazide, 128
DNA, 38, 165, 210
Dobutamine, 64—67
Domperidone, 270—271
Dopamine
  administration and toxicity of, 65
  for calcium channel blocker toxicity, 103
  decreased responsiveness to, 55
  esophageal ring contractions and, 268
  hemodynamic effects of, 62
  indications for and dose of, 63—65
  with norepinephrine, 60
  pharmacokinetics of, 63
  pharmacology of, 62—63
  renal effects of, 62—63
Dopamine receptors, stimulation of, 269
Dopaminergic receptors, inhibition of, 269
Doxapram, 234—238
Doxapram hydrochloride, 226
Doxorubicin, 199—200
Drug biotransformation, 16—30
Drug-biotransforming enzymes, hepatic tissue levels of, 30
Drug-metabolizing enzymes, in infants vs. adults, 11
Drugs
  accidental poisonings of children with, 12
  bioavailability of in adults vs. infants, 9—10
  in breast milk, 6—7, 9
  crossing placenta, 2
  effects of on older child, 11
  effects of on young child, 7—11
  fetal effects of, 8
  fetal exposure to, 2—6
  organ distribution of in adults vs. infants, 10
  overdose of, 222
  pharmaceutical consequences of at different developmental stages, 3
  physiocochemical characteristics of, 6
  routes and rates of conversion of, 16
  taken during pregnancy, fetal effects of, 4—6
Duodenal ulcer, 279
Dysrhythmias, 67, 77, 82, 94

E

EC2.8.2.1 enzyme, 27
Echocardiogram, 124—125
Effector cells, receptor density on, 52
Electrolyte depletion, 128—129
Embryo, 2—3, 36—37, 45—46
Enalapril, 134—135
Encainide, 94—95
Encephalopathy, 285
Encephalopathy syndrome, 282
Enzymes, 205—207
Enzymuria, 181
Eosinopenia, 208
Ephedrine, 7
Epinephrine, 55—58
Epipodophyllotoxins, 204, 205
Epoxide hydrolases, 24
Epoxides, 24, 27
Ergot, 4
Ergot alkaloids, 2
Erythropoietic depression, 164—165

Ethacrynic acid, 129, 149—150
Ethacrynic-cysteine complex, 150
Ethanol, 8, 226
Ethchlorvynol, 4, 227—228
Ethinyl estradiol, 4
Exchange transfusion, for iron toxicity, 305
Eye, 39,42
Eye expansion stage, 42

F

Ferrous sulfate, 7
Fetal drug exposure, 2—6
Fetal toxicity period, 37
Flecainide, 93—94
Fluid overload states, ethacrynic acid
 with, 149—150
Fluid therapy, 228
Flumazenil, 224
5-Fluorouracil, 4
Flurazepam, 222
Furosemide, 129
 adverse effects of, 147—148
 diuresis with, 212
 drug interactions of, 148—149
 fetal effects of, 4
 pharmacokinetics of, 146—147
 pharmacological actions of, 142—143
 during pregnancy, 146
 therapeutic uses of, 143—146

G

Gamma-aminobutyric acid (GABA), 224
Gas liquid chromatographic assays, 159
Gastric acid secretion, inhibited, 278
Gastric lavage, for iron toxicity, 300—301
Gastric scarring, 297
Gastroesophageal reflux, 270
Gastrointestinal hemorrhage, 273, 305
Gastrointestinal scarring, 305
Gastrointestinal system
 dialysis agents, 223, 228
 drugs for disorders of, 266—286
 iron toxicity in, 296—297
Gastrotomy, 304—305
Gentamicin, 11, 177—182
Glomerular filtration rate, 11, 99, 175
Glomerulonephritis, 149
Glucocorticoids, 22, 25
Glucose plasma levels, 247
β-Glucuronidase, 9
Glucuronidating transferases, xenobiotic, 26
Glucuronidation, 16, 25—27
Glucuronide esters, 163
Glucuronides, 24
Glucuronides, 24
Glucuronosyl transferase isozymes, 25—27
Glucuronosyl transferases, 25—26
Glutathione (GSH), 25, 27—28
Glutathione *S*-transferase, 25, 29
Glutethimide, 4, 228—229
Gonadal function, 211
Granulocytopenia, 192
Gray baby syndrome, 165—167
Gray-man syndrome, 99
Gray syndrome, 167
Griseofulvin, 4
Growth hormone stimulation tests, 189
Growth retardation, 3
Guanabenz, 132, 133
Guanafacine, 132
Guanethidine, 133
Guanfacine, 133
Guanidril, 133
Guanine nucleotides, 53
Gynecomastia, 276

H

H_1 receptor antagonists, pharmacology and
 toxicology of, 252—260
H_2 receptor antagonists, 275, 277
Haemophilus influenzae, 156—159, 168
Hageman factor, diminished activity of, 242
Haloperidol, 4
Halothane, 4
Heart contractility, 54
Heart rate, baseline, 54
Heavy metals, 3
Hematologic disorders, with chloramphenicol, 164—
 165
Hemodialysis, 227, 302, 305
Hemorrhagic hypotension, 56
Heparin, 4
Hepatic function testing, 191
Hepatic necrosis, 297
Heroin, 8
Hexylresorcinol, 7
High-performance liquid chromatographic assays,
 159
His-Purkinje conduction times, 92
His-Purkinje system, phases of action potential of, 77
Histamine, 252, 276
Hodgkin's disease, 198
Hormones, 207—209
Hydralazine, 134
Hydramine, for asthma, 255
Hydrocephalus, 44, 145—146
Hydrochlorothiazide, 4, 128
Hydrocortisone, 207
Hydrocortisone sodium succinate, 200
Hydrolases, 24
Hydrolytic reactions, in perinatal period, 24—25
Hydroperoxides, 27
7α-Hydroxylase activity, 22
Hydroxymethyl cimetidine, 274
5-Hydroxytryptamine, glucuronidation of, 26
5-Hydroxytryptamine-glucuronidating transferase,
 fetal, 26
Hydroxyurea, 4, 45, 210
Hydroxyzine, 4, 253, 255, 257

Hyperglycemia, 57, 89, 209
Hyperkalemia, 106, 124
Hyperparathyroidism, 281
Hyperphosphatemia, 282, 284, 285
Hypersensitivity reactions, 89, 180—181, 201
Hypertension
  in children, 118—122
    antihypertensive medications for, 128—136
    categorization of, 125—126
    causes of, 122
    diagnostic evaluation of, 123—125
    oral drugs in management of, 130—131
    systemic, management of, 126—128
  chronic, 127, 128
  classification of by age group, 122
  essential, 118—122
  laboratory tests for, 124—125
  medical history of, 123—124
  physical examination for, 124
Hypertensive crisis, management of, 126—127
Hypocalcemia, 302
Hypoglycemia, 56, 132
Hypoglycemic agents, 95
Hyponatremia, 204
Hypotension
  with barbiturate intoxication, 225
  with calcium channel blocker toxicity, 102—103
  norepinephrine for, 59—60
  with quinidine, 82
  treatment of, 228—229
Hypothermia, 227
Hypoventilation syndrome, congenital central, 236—237
Hypovolemia, furosemide-induced, 147

I

Ibuprofen, 242
Idoxuridine, 4
Ifosfamide (Isophosphamide), 195—196
Imipramine, 4
Immune suppression, 208—209
Indomethacin, 176, 245
  breast milk excretion of, 247
  fetal effects of, 5
  toxicity of
    following maternal ingestion of, 245
    following neonatal administration of, 245—247
Infants
  as distinct organism, 7
  drug absorption in, 8—9
  drug bioavailability in, 9—10
  drug effects on, 7—11
  drug-metabolizing enzymes in, 11
  drug therapy in, 8
  organ distribution of drugs in, 10
  susceptibility to adverse reactions in, 10
  urinary pH during sleep in, 9—10
Insensitivity period, 36
Insulin, 5, 63
Intragastric complexation, 303—304
Intravenous pyelogram, 125
Intraventricular hemorrhage, with indomethacin therapy, 246
Iodide, fetal effects of, 5
Iodine (radioactive), fetal effects of, 5
Ipecac, syrup of, 226, 300—301
Iron, 296
  content of products containing, 298—299
  elemental, 298
  toxic effects of, 296—297
    approaches to management of, 298—303
    chelation therapy for, 301—302
    controversies in management of, 303—305
    decontamination of, 300—301
    supportive care for, 302
    triage for, 298—300
Iron-binding capacity, total (TIBC), 300—302
Isoproterenol, 50
  administration and toxicity of, 61—62
  β-receptor stimulation with, 66
  indications for and dose of, 61
  inotropic response to, 53
  pharmacokinetics of, 61
  pharmacology of, 60—61
  for quinidine toxicity effects, 82—83
Isotretoin, 3

K

Kaliuresis, 148
Kidneys, dysfunction of, 164

L

Labetalol, 132
Lactational drugs, 6
Lactic acid concentrations, 297
Laparotomy, 305
Leukemia, 187, 210
Leukopenia, 204—205
Levodopa, 268, 269
Lidocaine, 86
  drug interactions of, 87
  electrophysiology of, 86—87
  half-life of, 278
  organ distribution of in adults vs. infants, 10
  pharmacokinetics and dosage recommendations of, 87
  toxicity of, 87—88
Lignocaine, 5
Lipophilic drugs, transplacental diffusion of, 2
Lithium, 3, 5
Liver, 163—164, 297
Loop diuretics, see Diuretics, loop
Lorazepam, 222
L-PAM, 195
Lung fluid accumulation, factors enhancing, 143
Lymphoblastic leukemia, acute (ALL), 187
Lymphoblasts, malignant, 206
Lymphocytopenia, 208
Lymphopenia, 192

Lysergic acid diethylamide, 8

M

Magnesium hydroxide, 303
Magnesium sulfate, 7
Malabsorption syndrome, 277
Malformations, 36, 37, 45—46
Mannitol, 212
Marijuana, 8
MC, as P450 isozyme inducing agent, 21
Mechlorethamine, 193—194
Meclizine, 5
Melanoma, malignant, 198
Melphalan, 195
Meperidine, 8, 255
Mephobarbital, 225
Mepivacaine, 5
Meprobamate, 5, 228—229
6-Mercaptopurine, 5, 190—191
Mescaline, 8
Mesonephros, 38
Messenger RNA, for P450 isozymes, 20—21
Metabolic acidosis, 297
Metalazone, 128
Metanephros, 38
Meta-O-dealkylated flecainide, 93—94
Methadone, 8
Methaqualone, 5
Methemoglobinemia, 88
Methotrexate, 5, 187—190, 206
Methoxyflurane, 5
3-Methoxy-*O*-demethyl encainide (3-MODE), 95
Methyldopa, 132, 133
Methyltestosterone, 5
Methylthiouracil, 5
Metoclopramidine, 266—270
Metolazone, 148
Mexiletine, 92—93
Microcytosis, aluminum-inflicted, 283
Microphthalmia, 38—43, 46
Midazolam, 222
Milk of Magnesia, 303
Minoxidil, 127, 134
Mitochondrial protein synthesis, 164
Mitocycin C, 5
Monocytopenia, 208
Monoethylglycine xylidide metabolite (MEGX), 87—88
Mono-*N*-dealkylated metabolite (MND), 85
Morphine, 8
Morphogenesis, 46
Morula, 36
Mucositis, 202—203
Muscarinic receptors, 252
Myelogenous leukemia, chronic, 196
Myeloid leukemia, acute, 191
Myelosuppression, 191, 197
  with ACT-D, 202
  with anthracyclines, 200
  with CDDP treatment, 213
  with dacarbazine, 199
  with procarbazine, 211
Myocardial depression, 100
Myocardial failure, dobutamine and, 66—67
Myocardial infarction, lidocaine treatment for, 87
Myocardial ischemia, 62

N

NAC, see *N*-Acetylcysteine
NAG, see *N*-Acetyl-β-glucosaminidase
NAPA, see *N*-Acetyl procainamide
Natriuresis, 148
Neisseria meningitidis, 157
Neonatal withdrawal syndrome, 255
Neopalium, growth rate of, 44
Nervous system, 43—45, see also Central nervous system
Netilmicin, 178
Neural tube, 43—44
Neurohumoral system, 54—55
Neurons, irreversible degeneration of, 41
Neurulation, 36
Neutropenia, 276
Nicotine, 8
Nifedipine, 99—100
  bioavailability of, 278
  dosage of, 102
  drug interactions of, 102
  for hypertension, 135
  for hypertensive crisis, 126—127
  pharmacokinetics of, 101
Nitrofuantoin, 5
Nitrogen mustards, 5, 192—196
p-Nitrophenol, 26
Nitroprusside drip, for hypertensive crisis, 126
Nitroreduction, 23
Nitrosoureas, 192, 197—198
Nonbarbiturate sedative hypnotic agents, toxicity with, 227—229
Norepinephrine, 53, 55, 58—60
Novobiocin, 5
Nursing, 6—7
Nystagmus, with phenytoin, 89

O

ODE, see *O*-Demethyl encainide
Ondine's curse, 236—237
Optic cup, 42
Optic vesicles, evagination stage of, 42
Oral contraceptives, 5
Organic chemicals, toxic effects of, 23
Organogenesis, 2—3
Osteomalacia, dialysis-induced, 285
Osteomalacic osteodystrophy, 283
Otitis media, treatment of, 255—256
Over-the-counter drugs, 7, 12
Oxidation reactions, in perinatal period, 17—23
Oxygen therapy, 202
Oxytocin, 5

P

P450IIA1 isozyme, 22
P450 isozymes, 16—21
P450IZ1 isozyme, 19—20
P450 reductase, 18—22
Pallium, rapid growth of, 44
Pancreatic insufficiency, 272
Pancreatitis, acute, 278
Paraldehyde, 5
Parathyroid hormone, 281—283
Patent ductus arteriosus (PDA), 142, 145, 147
Pediatric drugs, principles of therapy and toxicity of, 2, see also Drugs; specific agents
Pediatrics, antidysrhythmic drugs in, 77—106
Penicillamine, 5
Penicillin, organ distribution of in adults vs. infants, 10
Peptic ulcer disease, 209, 276
Perinatal periods
  conjugation reactions in, 25—29
  drug biotransformation during, 16—30
  hydrolytic reactions in, 24—25
  oxidation reactions in, 17—22
  reduction reactions and redox cycling in, 23—24
  for various species, 17
Peripheral neuropathy, 213
Peripheral plasma renin activity, 125, 126
Peripheral vasodilation, 100
Pharmacodynamics, definition of, 51
Pharmacokinetics, definition of, 50—51
Pharmacokinetic studies, limitations of, 16
Phencyclidine, 8
Phenobarbital
  fetal effects of, 5
  intoxication with, 226
  organ distribution of in adults vs. infants, 10
  as P450 isozyme inducing agents, 21
  quinidine and, 82
Phenylpropanolamine, 7
Phenytoin, 88
  chloramphenicol and, 168
  drug interactions of, 91
  electrophysiology of, 88—89
  fetal effects of, 5
  fetal exposure to, 3
  organ distribution of in adults vs. infants, 10
  pharmacokinetics and dosage recommendations of, 89
  protein binding of, 89
  quinidine and, 82
  toxicity of, 89
Phlebitis, 181
Pituitary-hypothalamic function, 189
Placenta, 2, 3
Plant products, 203—205
Platelets, 243—246
Platinum, 38, 212—213
Podophyllotoxins, 205
Podophyllum peltatum, 204
Polynuclear aromatic hydrocarbons (PAHs), 19—20
Potassium, 88, 175, 267
Potassium-sparing diuretics, 132
Practolol, 148
Prazepam, 222
Prazosin, 133, 148
Prednisolone, 207
Prednisone, 207—209
Pregnancy, 2—6, 146
Premature ventricular contractions (PVCs), suppression of, 90
Prenatal periods, 36—46
Procainamide, 83—85
Procarbazine, 5, 211
Progestins, 5
Prolactin, inhibition of release of, 63
Prolonged QT interval syndrome, 88
Promethazine, 255
Propafenone, 95—96
Propranolol
  fetal effects of, 5
  half-life of, 278
  for hypertension, 129, 132
  with lidocaine, 87
  organ distribution of in adults vs. infants, 10
  with tocainide, 91
  verapamil and, 102
Propylthiouracil, 5
Prostaglandin E excretion, 246
Prostaglandin synthetase, 243
Protein binding, 2
Protein synthesis inhibition, 207
Pseudoephedrine, 7
Pseudohypoaldosteronism, 146
Psychosis, with prednisone therapy, 209
Pulmonary abnormalities, edema-induced, 143
Pulmonary edema, 142—145
Pulmonary hypertension, 54, 63, 245
Pulmonary vasoconstriction, hypoxic, 60—61
Purkinje fibers, 86—87, 89, 93
Pyelonephritis, chronic, 125
Pyridoxine, 7

Q

Quinacrine, 5
Quinaglute, 81
Quinidine, 79—83, 105
Quinidine syncope, 82
Quinine, 5
Quinone/quinonoid structures, 23

R

Radioenzymatic assays, 159
Radionucleotide imaging, 125
Radionuclide ventriculograms, 200
Ranitidine, 276—279
Reactive oxygen species, 23
Redox cycling, 23—24
Reduction reactions, 23—24
Reflux esophagitis, 278

Regulation process, 36
Renal artery vasoconstriction, 57
Renal system, 125, 164, 246—247
Renal scan, 125
Renal tubular acidosis, 146
Renal ultrasound, 125
Renal vasoconstriction, 60
Renin-aldosterone system disturbances, 267
"Report of the Task Force on Blood Pressure Control in Children", 118
Reproductive system, altered development of, 3
Reserpine, 5, 133
Resin hemoperfusion, 227—228
Respiratory depression, drug-induced, 236
Respiratory distress syndrome (RDS), 142—144, 147
Respiratory system, doxapram effects on, 234—235
Reticulocytopenia, 165
Retinal folding, 43
Rhabdomyosarcoma, treatment of, 189
Rhombencephalon, 43
Rifampin, 82, 168

S

Salicylates, 7, 10
Salmonella, resistance of to chloramphenicol, 158
Salmonella typhi, resistant strains of, 157—158
Scopolamine, 5
Sedative hypnotic intoxication, 222—229
Septic shock, 65
Shigella dysenteriae, resistant strains of, 158
Sick sinus syndrome, 80
Sinus bradycardia, 98, 106
Sinus node, suppression of, 80
Sodium bicarbonate, 7, 303
Sodium depletion, 175
Sodium-potassium pump, ATP-dependent, 77
Sodium reabsorption, inhibition of, 142
Sphingomyelinase, age-dependent activity of, 182
Spironolactone, 105, 132
Staphylococcus, resistant strains of, 178
Status asthmaticus, 61
Steroid withdrawal, 209
Stockard's principles, 36—37
Stomatitis, 191
Streptococcus pneumoniae, 157
Streptomyces verticillus, 200—201
Streptomycin, wide use of, 177
Stress-induced ulcerations, 273
Stroke volume, 54, 67
Styrene 7,8-oxide, 28
Sulfate esters, 24
Sulfation, 27, 244—245
Sulfonamides, 5
Sulfonylureas, diltiazem and, 102
Sympathomimetic agents, 50, 99
Syndrome of inappropriate antidiuretic hormone secretion (SIADH), 194

T

Tachycardia, 94—96
Telencephalon, morphogenesis of, 44
Teratogenicity period, 36—37
Teratogenic response, 36
Teratogens, 36—38
Terazosin, 133
Testosterone hydroxylation, 22
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 19
Tetracyclines, 5
Thalidomide, 3, 5
Theophylline, 7, 10, 255
Thiazide diuretics, 128
6-Thioguanine, 191
Thiyl radicals, 23
Thrombocytopenia, 165, 196, 208, 276
Thyrotropin-releasing hormone, blunted response of, 63
Thyrotropin-stimulating hormone (TSH), inhibition of, 63
Tissue oxygen tension, reduction of, 23
Tocainide, 90—92
Tolbutamide, 5
Torsades de pointes, 82
Transient tachypnea of newborn (TTNB), 142, 145
Triamterene, 132
Triazene, 198, 199
Triazolam, plasma concentrations of, 275
Trimeprazine, 5
Trimethadione, 5
Triprolidine, 257
Tumor lysis syndrome, 210

U

UDPGA, 25
UDPG-dehydrogenase activities, 25
Uncoupling reaction, 53
Urinalysis, 124

V

Valproic acid, 5
Vancomycin, 178—183
Vasoconstriction, histamine-induced, 252
Vasodilators, 134
Ventricular arrhythmias, 106
Ventricular compliance, reduced, 54
Ventricular dysrhythmias, 87, 89, 90—92, 97, 98
Ventricular fibrillation, prevention of, 87
Ventricular tachycardia, 62, 94
Ventricular tachydysrhythmias, 96
Verapamil, 99—102, 126, 135—136
Vinblastine, 203—204
Vinca alkaloids, 203, 204
Vincristine, 6, 203—204
Vitamin A, fetal effects of, 7
Vitamin D, 7, 281—283
Vitamin K (Menadione), fetal effects of, 7

VM-26, 204—205
Vomiting, treatment of, 254—255
VP-16, 204—205

W

Warfarin, 6, 82
Wolff-Parkinson-White (WPW) syndrome, 83, 97, 105

X

Xanthines, methylated, 235—236, 238, 255
Xenobiotic biotransforming isozymes, 22, 29, 30
Xenobiotic-hydrolyzing hydrolases, 24
Xenobiotics, 6, 27
Xenobiotic substrates, 24, 25
Xenobiotic sulfating enzyme, 27

Y

Yersinia enterocolitica septicemia, 304

Z

Zinc deficiency, in microphthalmia, 43